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International Journal of Clinical Case Studies

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Case Report

Understanding Intricacy of Viral Prompted Oncogenesis

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Received Date: July 24 2024 | Accepted Date: August 14 2024 | Published Date: August 18 2024

Citation: Thyyar M Ravindranath, (2024), Understanding Intricacy of Viral Prompted Oncogenesis., *International Journal of Clinical Case Studies*,3(4); **DOI:**10.31579/2835-9291/020

Abstract:

Viral induced cancer is an unusual manifestation of viral infection. Although rare, early diagnosis and management prevent mortality associated with cancers of viral origin. The mechanism of cancer formation is complex, and many viral proteins interact with host tissues to induce cancer formation. A high index of suspicion in a susceptible host helps to further investigate and diagnose these various cancer types.

Keywords: viral infection; cancer; oncogenic proteins; virus host protein interaction; T-cells

Introduction

Although uncommon, in 2018, infections were responsible for causing 13% of all cancers, amounting to 2.2 million cases (De Martel et al., 2019). Oncogenic viruses that cause cancer include Epstein-Bar virus (EBV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Human T-cell Lymphotropic Virus-1 (HTLV-1), Human Herpesvirus-8 (HHV-8) also named as Kaposi Sarcoma Herpes Virus (KSHV), Human Papilloma Viruses 16 & 18 (HPV 16 & 18) and Merkel's cell carcinoma virus. Virus infection alone is not sufficient to cause cancer. Therefore, other factors such as genetics, environmental factors resulting in modifications in genes, chromosomal mutations and alterations, changes in the levels of tumor activators and suppressors, and harmful habits are essential in precipitating tumors.

Epidemiology:

Among oncogenic viruses, EBV is a prolific infector, infecting close to 90% of humans. EBV transmission from person to person is through coughing, sneezing, or through sharing drinks and utensils. The EBV genome contains a double-stranded DNA and belongs to the ɤ-herpes virus. It is responsible for 1.5% of all cancers worldwide (Farrell, 2019). It causes cancers of the nasopharynx, gastric cancers, Burkitt lymphoma, and Hodgkin's lymphoma (Young et al., 2016). EBV causes lytic and latent phase infection and latent phase is responsible for EBV induced cancers.

Whereas HBV is a partial double-stranded enveloped virus, HCV is a single-stranded RNA virus. The former can integrate its DNA into the host cell and express viral oncogenes (Ringelhan et al., 2017), but the latter fails to do so producing cancer with the help of viral and host factors (Tashiro, Brenner, 2017). Both are responsible for 75-85% of hepatocellular cancer of the liver. Both are spread by unprotected sex, childbirth, and sharing needles used to inject drugs. HBV infection is prevalent in Sub-Saharan Africa and East Asia and HCV is predominant in Central Asia, East Asia, and North Africa. There is a vaccine against HBV, however a vaccine for HCV does not exist.

HTLV-1 is an enveloped, single stranded, diploid RNA virus that is endemic in Southwest Japan, Australia, Africa, and the Caribbean Islands. It is spread by unprotected sex, sharing needles used for injecting drugs, and infected pregnant mothers can pass it on to the fetus. 4-7% of HTLV-1 infection can result in Adult T-cell leukemia and Lymphoma [ATLL] (Coffi, 2015). HTLV-1 can infect T-cells of both CD4+ and CD8+ subtypes, dendric, and B-cells.

HHV-8 is a double stranded, enveloped DNA virus that exists in a latent form. It is spread by sexual contact and via blood and saliva. HHV-8 is prevalent in Southern and Eastern Africa and is associated with Kaposi Sarcoma. The incidence of Kaposi Sarcoma is 1 in 100, 000 in those that have infection with HHV-8 and is 5% in those who also have HIV (Facciolà et al., 2017).

HPV is a double stranded, circular, non-enveloped DNA virus that is responsible for 70% of not only cervical cancer, but also oropharyngeal, anal, vulva, vaginal, and penile cancers (Kobayashi et al, 2018). It is spread by touch and by sexual contact. Prevention is by vaccination against HPV infection. HPV burden of infection in the US is forty-two million persons infected with disease-associated HPV and thirteen million persons acquire a new infection (Lewis et al., 2021).

To induce tumors, oncogenic viruses develop unique interactions with host proteins resulting in virus-host protein interactions. A host body develops defense against cancer induced by viruses through adaptive immune responses, consisting of cellular response via T-cells and humoral response via B-cells through the production of antibodies. T-cells recognize antigens on the surface of viruses and annihilate viral particles before they can replicate.

Human Immunodeficiency Virus (HIV) by itself does not cause cancer but is a risk factor for several cancer types.

Mechanism of cancer formation:

Pathological response of the host tissue starts at the time of viral infection. It involves viral dysregulation of cell signaling, inducing oncoproteins [table] (Vélez-Bohórquez et al., 2018) that are autonomous in replication and adaptation, oblivious to inhibition and apoptotic signals, and to angiogenesis, tissue assault, and metastasis (Nikitin et al., 2012).

In hepatocellular carcinoma, induction is via, 1. inflammatory processes involving the Transforming Growth Factor – β (TGF-β) which activates c-Jun N- (JNK) terminal kinase of the mitogen activated protein kinase (MAP) family; resulting in rapid cell proliferation and decreased genetic mending, 2. inflammatory cytokines such as Interleukin-6 (IL-6), Tumor Necrosis Factor -α (TNF- α), and Iterleukin-1β (IL-1 β) promote resistance to apoptosis and activate the JNK pathway. This results in the generation of reactive oxygen species that inhibit apoptosis (Tarocchi et al., 2014), 3. Insertion of viral DNA into the host genome results in genome instability, amplification, deletion, and the translocation of chromosomes, 4. Products of viral proteins inhibit apoptosis. Aberrant methylation inhibits tumor suppressors.

The role of micro RNAs:

Both HBV and HCV use micro RNAs to induce tumorigenesis. Interactions between viruses and micro RNAs, which are non-coding particles, result in the inhibition of tumor suppressor and the dysregulation of cell motility (Qiao et al., 2017).

Merkel's carcinoma virus, which causes an aggressive skin cancer in immunocompromised hosts through two oncoproteins, stimulates proliferation and induces cell cycle progression and transformation (Chang, Moore, 2012).

HPV, through its proteins, induces loss of control during the cell cycle and the activation of a signaling cascade that leads to uncontrolled cellular proliferation and differentiation (Tomaic, 2016).

Immunocompromised state:

These patients have more viral copies that lead to damage to DNA with the inability to repair and inhibition of apoptosis which encourage cancer induction (Reusser, 2015).

Prevention:

Effective vaccine strategy exists for viruses such as HBV which has decreased the carrier rate for HBV. Vaccination against HPV could reduce the incidence of cervical cancer by 70-90%.

Management:

Other management strategies include therapy directed towards specific cancer types with immunotherapy and chemotherapy.

Conclusion

Although cancers induced by viral infection are uncommon, it requires a clinician's alertness and an elevated level of suspicion to detect them in high-risk individuals such as those who are immunocompromised and those who are unvaccinated against certain oncogenic viruses prior to infection. The mechanism of cancer induction is complex, and treatment involves cancer management with the help of an Oncologist.

Viral type	Cancer inducing viral element	Consequence on host cells
Hematolymphoid		
Epstein Barr	EBNA1	c-MYC translocation, proliferation, proinflammatory cytokines, prevents degradation of proteosome and antigen presentation, facilitate degradation of p53.
	EBNA3C	Cell immobilization
	LMP1	Dysregulation of apoptotic pathway and proliferation, NK cell activation, uncontrolled proliferation, downregulate tumor suppressor.
	E2	Proliferation
Hepatitis C	E2	Proliferation
	unknown	Antiapoptotic, reduces caspase activity
	NS3 y E7	IL-2, IL-10 increases somatic hypermutation, translocation 14-18 overexpression of BLC-2
Herpes 8	vCyc	Integrates the host genome and generates cell expansion
HTLV-1	Tax	Recruits' transcription factors, activates NF-κβ and AKT pathways leading to proliferation, accelerates cell cycle, cause structural DNA damage, inhibits repair, produces overduplication of centrosomes
	HBZ	Activate alternate NF-κβ involved in cell proliferation, promotes transcription factor E2F1 and proliferation, increases the viral load and the action of telomerase
Epithelial Cells		
Epstein Bar	EBNA1	Protooncogene c-MYC translocation, proliferation, DNA methylation, p16 suppression
	LMP1	Activate p13k y BCR, deregulates apoptotic pathway and proliferation
Hepatitis B & C	Pre-S2 deletion mutant proteins	TGF-β, IL1-β, TNF-α active JNK that increases the rate of cell proliferation
	STAT3 y NF-kB	Antiapoptotic and regulate tumor angiogenesis
	Viral protein HBx	Activates mitogenic signals, generates chromosomal instability, increased metalloproteinase matrix production, which facilitates cell migration
	Viral protein HBVs	Mitochondria: inhibits JTB by increasing the life of the cell and preventing apoptosis
	Unknown	miR602: inactivation RASSF1A

Hepatitis C	FNDC3B	Codifies a product that facilitates cell motility and metastasis
Merkel	T (large) antigen	Bind pRB, active proliferation
	T (small) antigen	It binds and reprograms PP2A, promotes cell cycle and transformation
HPV	E6	Degrade p53, with deregulation
	E7	Degrade pRB, Suppression of miR203 that activates TP63 by promoting proliferation, Induces telomerase activity, increasing the life of keratinocytes
	Unknown	miR100: inhibits PLK1 gene, promotes early carcinogenesis
Mesenchymal		
Epstein Barr	EBNA 1	Protooncogene translocation c-MYC (8-14), proliferation
Herpes 8 - Kaposi	LANA-1	Inhibit p53 y pRB
	Prox-1	Causes lymphoendothelial differentiation
	vFLIP	Induces endothelium-mesenchymal transition. Responsible for fusiform morphology
	kaposins A, B, C y ORF K1	Tumorigenesis promoter
	miR-K12-1	Arrest p53
	miR-K12-3 y miR-K12-7	Active secretion of IL6 and IL10, which promote cell growth, angiogenesis and suppression of T cells

Table: Viral Proteins Involved in Oncogenesis.

EBNA1: Epstein Barr Virus nuclear antigen-1, c-MYC: Cellular myelocytomatosis oncogene, p53: tumor suppressor gene, EBNA3C: Epstein Barr Virus nuclear antigen 3C, LMP 1: Latent Membrane Protein 1, NK-cell: Natural Killer cell, E2: elimination reaction, NS3 y E7: Non-structural protein 3 and HPV E7 protein, IL-2: Interleukin-2, IL-10: Interleukin-10, BCL-2: B-Cell Leukemia/Lymphoma 2, AKT=PKB: protein kinase B, vCyc: viral cyclins, Tax: , HBZ: HTLV-1 basic leucine zipper factor (HBZ), E2F1: E2 promoter binding factor 1, p16: cyclin-dependent kinase inhibitor, Pre-S2 deletion mutant proteins: The Pre-S2 Domain of the Hepatitis B Virus, TGF-β: Transforming Growth Factor- β, IL1-β: Interleukin 1- β, TNF-α: Tumor Necrosis Factor- α, JNK: c-Jun N-terminal kinases, JTB: Jumping Translocation Breakpoint, active JNK p13k y BCR: P13 kinase B-cell antigen Receptor, STAT3 y NF-kB: signal transducer and activator of transcription 3 Nuclear factor kappa beta, HBx: HBV-encoded oncogene X protein, mir602: microRNA-602, RASSFA1: Rat Sarcoma Virus-association domain family 1A, FNDC3B: Fibronectin Type III Domain Containing 3B, , T (large) antigen: large T antigen, T (small) antigen: small T antigen, PP2A: Protein phosphatase 2, E6: oncoprotein, E7: Human Papilloma Virus oncogene, pRB: Retino Blastoma Protein, mir203: mcicro RNA 203, TP63:tumor protein p63, mir100: micro RNA 100, PLK1: Serine/threonine-protein kinase, LANA-1: latent nuclear antigen, p53 y pRB: tumor protein p53 gene retinoblastoma protein (pRb), prox-1: Prospero homeobox gene 1, vFLIP: Viral FLICE inhibitory proteins, y ORF K1: membrane protein, p53: a tumor suppressor protein, miR-K12-1: micro RNA K12-1, mir-k12-3 y: micro RNA k12-3y, mir-k12-7: micro RNA-k12-7, IL-6: Interleukin-6, IL-10: Interleukin-10, T cells: Thymus derived cells.

Acknowledgement: Author would like to thank Malini Ravindranath PhD for her editorial guidance.

Conflict of Interest: None

Funding: None

Ethical Approval: Not applicable

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