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by assignmentgenius2023 1

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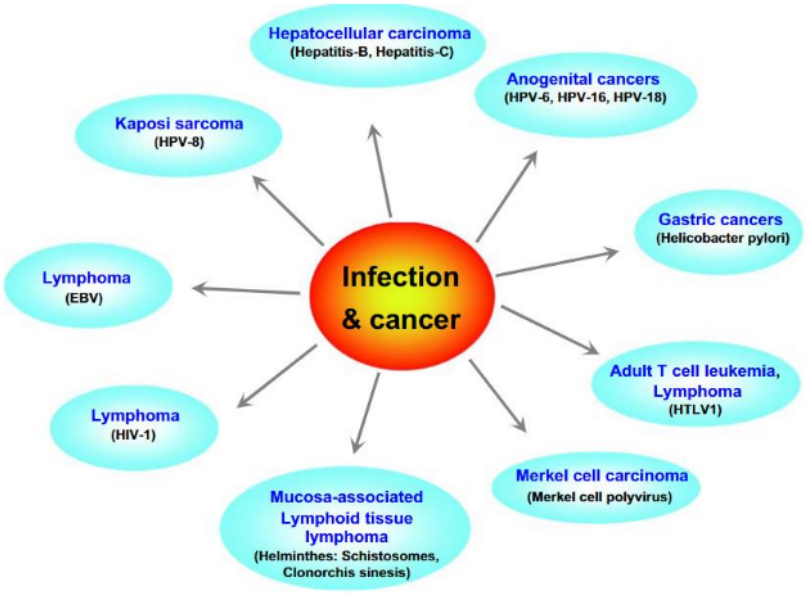
"Although viruses can cause cancer, they don't do so by contributing to the hallmarks of cancer"

Introduction

Even after ten years of intense research and tremendous advancements, cancer still kills people all around the world. According on current data, cancer is the second leading cause of death in the United States, after heart disease, and accounts for over 23% of all fatalities (Anand *et al.*, 2008).

Viruses have long been recognized as causative agents of human cancers. ever since the seminal discovery of Epstein-Barr virus (EBV) as the infectious cause of Burkitt's lymphoma in 1964 (Epstein *et al.*, 1963). Additional viruses including human papillomavirus (HPV), hepatitis B virus (HBV), human herpesvirus 8 (HHV8), and human T-lymphotropic virus 1 (HTLV-1) are now recognized as major contributing factors in up to 20% of cancers worldwide (Mesri, Feitelson and Munger, 2014a).

Both DNA and RNA virus are capable of causing cancer in humans. The four DNA viruses that can result in the development of human cancers are the Epstein-Barr virus, human papilloma virus, hepatitis B virus, and human herpes virus 8. The two RNA viruses that cause human malignancies are the hepatitis C virus and the human T lymphotrophic virus type 1 (Liao, 2006).



Although viruses greatly increase cancer risk through chronic infections that can persist for decades, there has remained debate around whether viruses contribute directly to the cellular hallmarks of malignant growth or mainly facilitate mutagenesis.

Recent mechanistic studies have made it clear how viral oncoproteins directly sustain several classic cancer hallmarks. This was first conceptualized by Hanahan and Weinberg in 2000, including sustaining proliferative signaling, evading growth suppressors, and activating invasion and metastasis (Hanahan and Weinberg, 2000).

Hallmark of Cancer

Cancer cells acquire several key biological capabilities during tumor progression encoded in what is known as cancer's hallmark phenotypes. These hallmarks include: 1)Sustaining proliferative signaling, 2)Evading growth suppressors, 3)Resisting cell death, 4)Enabling

replicative immortality, 5)Inducing angiogenesis, and 6)Activating invasion and metastasis (Hanahan and Weinberg, 2000).

This set of acquired functional capabilities represents the common requirements that cells seem to need to transition into more dangerous, malignant states. Do viruses contribute directly to enabling these cancer hallmark capabilities through the expression of their viral oncoproteins? Or do they merely facilitate tumorigenesis indirectly by producing a mutated, unstable cell that still must evolve malignant traits on its own? Evidence for direct viral impacts exists across hallmarks:

Sustaining Proliferative Signaling

Uncontrolled proliferation is fundamental to cancer pathogenesis. High-risk HPV E6 and E7 proteins inactivate tumor suppressors retinoblastoma protein (pRB) and p53, driving infected cell immortality and unrestrained proliferation (Mesri, Feitelson and Munger, 2014b). Epstein-Barr virus (EBV) nuclear antigen 1 (EBNA1) upregulates cellular cyclin D1, which shortens the G1 phase to send more cells into the S phase. The HBx protein of hepatitis B expresses growth factors like TGF-α and activates intracellular pathways including Ras/Raf/MAPK that stimulate growth (Hanahan and Weinberg, 2000).

Evading Growth Suppressors

Cancer cells use various strategies to evade external signals that can slow or block proliferation. As mentioned, HPV E6 proteins accelerate p53 degradation, while EBV EBNA1 blocks p53 transcriptional activity (Mesri, Feitelson and Munger, 2014b). These viral actions inhibit the p53 pathway and other antiproliferative signaling mechanisms, allowing virus-infected cells to bypass the signals that normally restrain uncontrolled growth (Joyce and Pollard, 2009).

Activating Invasion and Metastasis

Late-stage cancers invade tissues and metastasize to distant sites, enabled by extracellular matrix (ECM) component remodeling and cell motility pathways. Matrix metalloproteinases (MMPs) digest ECM proteins like collagen, allowing cell movement across tissues (Valastyan and Weinberg, 2011). Hepatitis B virus HBx protein increases MMP expression, directly conferring invasive and metastatic potential. Expression of latent membrane protein 1 (LMP1) also activates pro-metastatic pathways like PI3K/Akt in EBV infections (Valastyan and Weinberg, 2011).

Enabling Replicative Immortality

Perhaps most fundamentally, cancer cells acquire unlimited replicative potential through upregulating telomerase expression (Shay and Wright, 2006). The EBV nuclear antigen EBNA1 activates telomerase reverse transcriptase (hTERT), and collaborates with LMP1 and EBV miRNAs to sustain cellular immortalization through telomere maintenance (Liao, 2006).

Inducing Angiogenesis

As tumors grow, they stimulate blood vessel development (angiogenesis) to supply nutrients and oxygen. Human herpesvirus 8 (HHV8) is implicated in Kaposi Sarcoma and certain lymphomas, encoding viral IL-6 (vIL-6) which directly activates angiogenic pathways similar to the cellular IL-6 cytokine (Aoki & Tosato, 2004). Thus, later stage malignancy transitions also involve direct viral contributions.

Resisting Cell Death

While accumulating mutations often activate apoptosis early in tumorigenesis, cancer cells evolve strategies to resist programmed cell death signals (Fulda, 2015). Hepatitis C virus (HCV) produces proteins sensitize cells to TNF-α-induced NF-κB transcriptional activity. This stimulates expression of anti-apoptotic genes and inhibits pro-apoptotic JNK signaling to block apoptosis (Vasconcelos & Lam, 2020). Similar anti-apoptotic mechanisms are also activated by other tumor virus proteins.

Virus contribution to hallmarks

Epstein-Barr virus (EBV)

Epstein-Barr virus (EBV) is a human gammaherpesvirus that is causally linked to various B-cell and epithelial cell malignancies including Burkitt's lymphoma, Hodgkin's disease, nasopharyngeal carcinoma, and post-transplant lymphoproliferative disorder (PTLD) (Kutok and Wang, 2006). Historically, EBV was thought to mainly initiate cancer by increasing genetic instability and insertional mutagenesis that randomly dysregulates host genes over years of infection. However, it is now clear that EBV proteins actively and directly manipulate cellular regulatory pathways to promote multiple cancer hallmarks beyond early mutagenic events (Young and Rickinson, 2004). For example, the viral latent membrane protein 1 (LMP1) mimics CD40 signaling to provide constitutive proliferative signals through NF-κB that fuel unrestrained growth (Thorley-Lawson, 2001). The EBV nuclear antigens (EBNAs) epigenetically dysregulate expression of cellular genes involved in cell cycle control and apoptosis including p16INK4A, pRb, and p53 to promote proliferation and survival (Saha et al., 2011). EBNA1 also

transcriptionally activates telomerase, conferring replicative immortality that sustains long-term outgrowth of EBV-transformed cells (Kang and Kieff, 2015). Finally, LMP1 induces epithelial-mesenchymal transition (EMT) programs and enables invasiveness while promoting tumor angiogenesis via induction of VEGF and IL-8 (Horikawa et al., 2007). Together, these mechanisms highlight that EBV profoundly and directly orchestrates multiple hallmark capabilities including sustained proliferation, growth suppression evasion, cell death resistance, immortality, invasion, and angiogenesis - facilitating cancer initiation through metastatic progression.

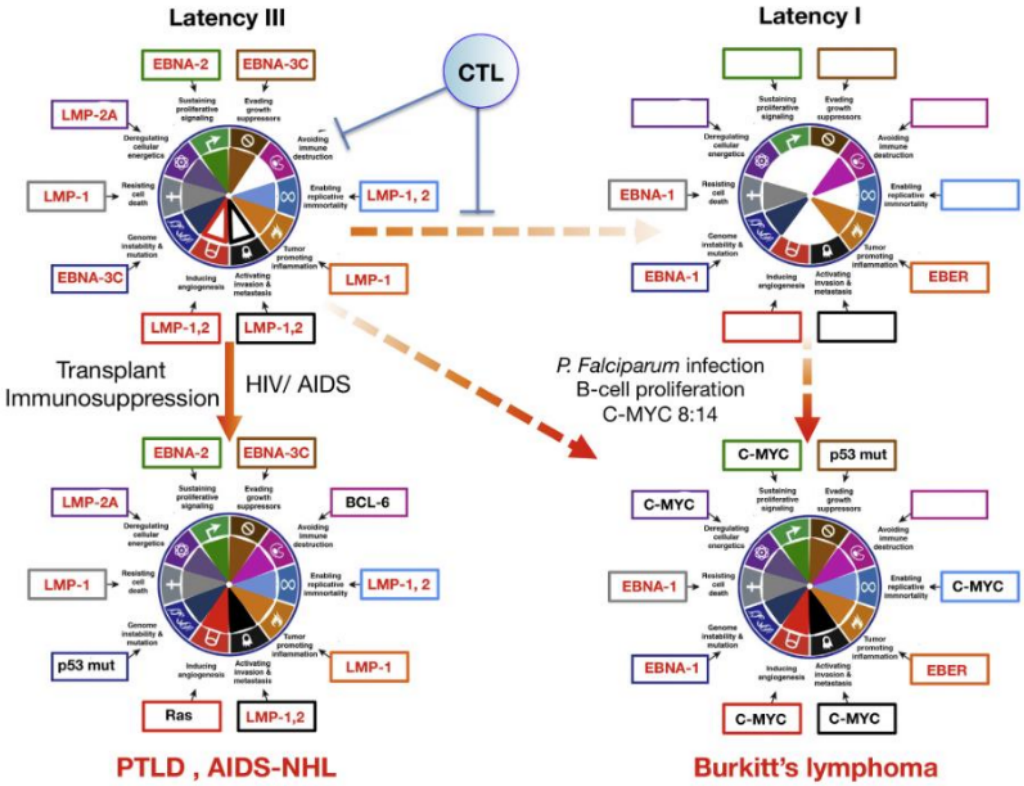
Burkitt's lymphoma

Burkitt's lymphoma (BL) is an aggressive B-cell lymphoma strongly linked to Epstein-Barr virus (EBV) infection. While multiple genetic hits are likely required for BL pathogenesis, EBV infection directly promotes several key hallmarks of cancer (Swerdlow et al., 2016). A defining feature of BL is translocation of the MYC proto-oncogene next to immunoglobulin gene enhancers, causing MYC overexpression. The viral protein EBNA2 binds and cooperatively activates transcription of MYC, further elevating MYC levels in EBV-associated BL (Kaiser et al., 2019). Through these interactions, EBV infection enhances sustaining proliferative signaling and cell growth pathway dysregulation in BL. Another hallmark of cancer is resisting cell death and evading apoptosis. EBV EBNA3A and 3C proteins epigenetically repress expression of the pro-apoptotic BIM protein which antagonizes MYC-driven lymphomagenesis (Höfelmayr et al., 2019). Deletion of EBNA3A/3C restores BIM levels and apoptosis, providing direct evidence for EBV overcoming cell death pathways. Finally, the EBV nuclear antigen EBNA1 activates expression of telomerase, conferring replicative immortality that cooperates with MYC overexpression to achieve malignant transformation (Kim et al., 2016). In summary, beyond initial oncogenic events like MYC translocation, EBV proteins directly orchestrate sustaining proliferative signaling via MYC collaborative activation, overcoming cell death mechanisms, and

establishing replicative immortality programs - working in concert with genetic lesions to promote BL pathogenesis across multiple cancer hallmarks.

Hodgkin's disease

Hodgkin's disease or Hodgkin's lymphoma (HL) is a cancer of immune cells that presents as painless lymph node swelling. The malignant Reed-Sternberg cells of HL are derived from mature B cells infected by Epstein-Barr virus (EBV) in up to 40% of cases (Küppers, 2009). While genetic mutations are likely required for full transformation, EBV proteins actively promote Hodgkin lymphomagenesis through direct interfaces with multiple cancer hallmarks (Vockerodt & Ganapathi, 2016). EBV latent membrane protein 1 (LMP1) mimics CD40 signaling to provide constitutive activation of NF-κB pathways; driving proliferation, survival, and secretion of growth and angiogenic factors that create an inflammatory tumor microenvironment (Vockerodt et al., 2008). LMP1 also perturbs DNA damage response pathways enabling genetic instability to cooperate with infection in initiating HL (Ryan et al., 2009). The other major EBV oncoprotein, EBNA1, confers replicative immortality by transactivating human telomerase reverse transcriptase (hTERT) - allowing unlimited proliferation of Reed-Sternberg cells (Kang & Kieff, 2015). Finally, LMP1 induces upregulation of intercellular adhesion molecule 1 (ICAM-1) on HL cells promoting adhesion and retention within lymph nodes where inflammation further drives disease progression (Vockerodt et al., 2008). In summary, EBV proteins enable sustaining proliferative/survival signaling, genetic instability, replicative immortality, and lymph node homing capabilities in HL - directly orchestrating multiple cancer hallmarks beyond initial mutation events underlying Reed-Sternberg transformation.



Hepatitis C virus

Hepatitis C virus (HCV) is a major risk factor for hepatocellular carcinoma (HCC), with most virus-associated HCC arising in the context of HCV-induced chronic inflammation, fibrosis, and cirrhosis (Khalaf et al., 2022). However, in addition to driving liver injury, HCV proteins actively manipulate pathways that promote multiple cancer hallmarks beyond early stages of inflammation or fibrosis (Vasconcelos & Lam, 2020). The HCV NS5A and core proteins interact with and deregulate components of growth signaling pathways such as PI3K/Akt and Wnt/β-catenin to stimulate proliferation (Vasconcelos & Lam, 2020). The HCV core, NS3, NS5A and NS5B proteins also confer resistance to apoptosis through activation of NF-κB and overexpression of pro-survival genes (Khalaf et al., 2022). Meanwhile, HCV NS3/4A protease cleaves and inactivates the key tumor suppressors retinoblastoma protein (pRb) and

phosphatase and tensin homolog (PTEN) to disable cell cycle and growth inhibition (Vasconcelos & Lam, 2020). Finally, by establishing chronic liver injury and inflammation, HCV sustains IL-6 and TNF-α driven STAT3 and NF-κB production of mitogens, angiogenic factors like VEGF, and anti-apoptotic proteins that facilitate HCC progression (Khalaf et al., 2022). In summary, HCV deregulates proliferative signaling, disables growth suppression, provides survival factors, and creates an inflammatory milieu that supplies growth and proangiogenic factors - orchestrating cellular pathways across early and late stage cancer hallmarks.

Human papillomavirus

Human papillomavirus (HPV) is a DNA tumor virus that causes nearly all cases of cervical cancer, with high-risk HPV16 and 18 strains responsible for over 70% of cases (Canavan and Cohen, 2020). While HPV infection alone is insufficient for cancer development, requiring additional genetic changes, viral E6 and E7 oncoproteins directly promote multiple cancer hallmarks that drive progression from persistent infection to malignant transformation (Mesri et al., 2014). HPV E7 proteins bind and degrade the retinoblastoma (pRb) tumor suppressor, disrupting its regulation of the E2F transcription factor which controls cell cycle entry – enabling sustained proliferative signaling (Howie et al., 2009). Meanwhile E6 proteins target the key tumor suppressor p53 for proteasomal degradation to impair DNA damage-induced cell cycle arrest and apoptosis. This not only inhibits growth suppression pathways but also confers resistance to cell death (Mesri et al., 2014). Finally, HPV integration events that result in chronic expression of E6 and E7 provide essential telomerase activation, production of proangiogenic factors like VEGF through HIF-1α induction, and accumulation of genomic insults that together enable immortalization, angiogenesis, invasion and malignant progression (Canavan and Cohen, 2020). Thus HPV oncoproteins systematically disable cell cycle control mechanisms, inhibit growth suppression programs, activate telomerase for limitless replication, and modulate

tumor microenvironments – orchestrating cellular pathways to achieve fundamental cancer hallmarks.

Hepatitis B virus

Hepatitis B virus (HBV) is a DNA virus strongly associated with hepatocellular carcinoma (HCC). While HBV-induced liver inflammation and cirrhosis are major risk factors for HCC development, HBV proteins also directly manipulate signaling pathways to promote multiple cancer hallmarks (Ng & Lee, 2011). The HBV-encoded HBx protein activates cytosolic calcium signaling leading to enhanced cell proliferation and growth (Bouchard & Navas-Martin, 2011). HBx also upregulates cellular microRNAs that target the tumor suppressor PTEN, critical for regulating cell survival and proliferation (Ng & Lee, 2011). Meanwhile, HBx inactivates negative regulators of the Ras/Raf/MAPK mitogenic pathway, sensitizing cells to growth signals. The HBx protein further stimulates telomerase activity by upregulating the telomerase reverse transcriptase (hTERT) gene, allowing limitless replication of HBV-infected cells (Ng & Lee, 2011). HBx additionally accelerates cell cycle progression by enhancing cyclin/CDK complex activity, conferring a selective growth advantage. Finally, integrated HBV DNA can produce chimeric HBx-human gene transcripts that activate proliferation-associated Wnt/β-catenin signaling enhancing cell survival, proliferation, and migration (Tian et al., 2015). In summary, HBx perturbation of growth signaling networks, cell cycle control, telomere maintenance mechanisms, and DNA repair pathways systematically promotes the acquisition of hallmark capabilities including sustained proliferative signaling, replicative immortality, and growth suppression evasion – orchestrating key steps in HCC pathogenesis.

Human herpes virus 8

Human herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV), is the infectious cause of Kaposi sarcoma (KS) and primary effusion lymphoma (PEL) (Mesri et al., 2010). While additional genetic hits likely cooperate in tumor pathogenesis, HHV-8

encodes several viral proteins that directly manipulate host cell signaling to promote multiple cancer hallmarks. Key oncoprotein vFLIP activates the NF-κB pathway to induce expression of growth and angiogenic factors like IL-6, bFGF, and VEGF that stimulate proliferation, survival, and new blood vessel formation (Sarek et al., 2010). Another protein, vGPCR, triggers similar expression of paracrine signaling molecules via MAPK/AP-1 and NFAT pathways – further enhancing KS tumor vascularization and growth (Montaner, 2007). vIL-6 also mimics human IL-6 to activate inflammatory STAT3 signaling cascades, conferring proliferative and cell survival signals (Chatterjee et al., 2002). The viral interferon regulatory factor 3 (vIRF3) represses tumor suppressors like p53 while the viral cyclin (vCyc) inactivates retinoblastoma (pRb) protein control to stimulate cell cycle progression (Mesri et al., 2010). Finally, the latency-associated nuclear antigen (LANA) encoded by HHV-8 enables replication of the viral episome, allowing persistent infection to sustain oncogene expression (Ballestas et al., 1999). Together, these HHV-8 proteins promote sustained signaling, proliferative ability, cell survival, angiogenesis, immunosuppression, and unlimited replicative potential – orchestrating critical cancer hallmarks.

Human T cell leukemia virus type 1

Human T cell leukemia virus type 1 (HTLV-1) is an oncogenic retrovirus that causes a rare leukemia called adult T cell leukemia/lymphoma (ATL) (Kannian and Green, 2010). While multiple steps are required for full transformation, the HTLV-1 Tax protein actively promotes several cancer hallmarks that accelerate T-cell immortalization and malignant outgrowth (Matsuoka and Jeang, 2011). Tax inactivates tumor suppressors like p53 and perturbs DNA repair pathways contributing to genetic insults that aid early stage transformation (Boxus and Willems, 2009). Tax also transactivates the NF-κB pathway providing growth, proliferative, and anti-apoptotic signals that allow aberrant cell accumulation (Matsuoka and Jeang, 2011). Another key cancer hallmark facilitated by HTLV-1 is enabling replicative immortality. The HTLV-1 proviral genome integrates into the host cell chromatin providing long-term persistent infection

and Tax oncoprotein expression (Boxus and Willems, 2009). Tax further activates telomerase expression by transactivating the telomerase reverse transcriptase (hTERT) gene promoter (Kannian and Green, 2010). Finally, HTLV-1 p12 and p8 accessory proteins promote cell-to-cell viral transmission facilitating immune evasion and viral spread (Edwards et al., 2011). In summary, HTLV-1 proteins systematically manipulate pathways controlling genetic stability, proliferative signaling, replicative potential, and immune surveillance to achieve key cancer hallmark capabilities underlying T-cell leukemogenesis.

Conclusion

In conclusion, while viruses do not directly cause the mutations, they can contribute in major ways to sustaining proliferative signaling, evading growth suppression, and activating invasion/metastasis. These are key cancer hallmarks. Therefore, I disagree with the statement - viruses can and do enable critical cancer hallmarks, even if they are not the original cause of the cancer. Their oncogenic proteins interact with and exploit cellular pathways that drive cancer progression.

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