21st Century Publisher

21 ST CENTURY PATHOLOGY

21st Century Pathology

Review Article

Open Access

Carcinogenesis and Leukemogenesis of Microorganisms: A Review

Cameron K. Tebbi

Children's Cancer Research Group Laboratory, United States of America

***Corresponding Author:** Cameron K. Tebbi, Children's Cancer Research Group Laboratory, 13719 North Nebraska Avenue, Suite # 108 Tampa, Florida 33613-3305, United States of America; E-mail: ctebbi@childrenscancerresearchgrouplaboratory.org

Received: 16 January 2021; **Accepted:** 24 February 2022; **Published:** 28 February 2022

Abstract

Several studies have shown that microorganisms can affect tumor initiation and progression, directly through their effects on the cells and indirectly by their effects on the immune system. The carcinogenesis of certain viral, bacterial, fungal, and parasitic organisms has been long suspected. Additionally, the direct association of some viral agents and cancer such as Epstein-Barr virus and Burkitt's lymphoma, in certain geographical areas, have been reported. Likewise, the development of non-cardia gastric cancer by Helicobacter pylori and the relation of infection with Schistosoma haematobium and the development of bladder cancer is well recognized. Studies regarding the carcinogenetic effects of fungal infections have been mostly attributed to their mycotoxin production. Recent recognition that some filamentous fungi and yeasts potentially play a role in the development of certain cancers has expanded understanding of the scope of their involvement in carcinogenesis. Most recently, it has been shown that plasma of patients with B-cell acute lymphoblastic leukemia in full remission, and long-term survivors, immunologically react to the products of a mycovirus containing Aspergillus flavus. Unlike controls, in vitro exposure of mononuclear leukocytes from these patients to the products of this organism was shown to reproduce genetic and cell surface phenotypes characteristic of B-cell acute lymphoblastic leukemia. The potential carcinogenic and leukemogenic role of fungi, with and without mycoviruses, needs further investigation.

Keywords: *Bacteria; Cancer; Carcinogenesis; Etiology; Fungi; Parasites; Leukemogenesis; Mycoviruses; Viruses*

Highlights

Carcinogenic effects of certain microorganisms, including viral, bacterial, fungal and parasitic agents have long been suspected.

• Several studies have revealed diverse biological pathways to the carcinogenesis of microorganisms, including presence of viral gene products in some cancer and precancerous cells.

• Recent reports indicate the presence of antibodies to a certain mycovirus-containing Aspergillus flavus in the plasma of B-cell acute lymphoblastic leukemia (ALL) patients in complete remission. Exposure of mononuclear leukocytes of these ALL patients to the products of the above organism, in vitro, had resulted in the redevelopment of typical genetic and cell surface phenotypes of ALL. These findings are of interest and need to be further explored.

Introduction

For a long, association of certain viral, bacterial, fungal, and parasitic infections and the development of cancer has been suspected, but in most cases, not definitively proven. Some estimate that worldwide, approximately 20% of all cancers are induced by various infections [1]. While the association of certain infections and malignant disorders is well established, the mechanisms governing these processes are often poorly understood. In 2008, an association of infections and cancer was reported to range from 3.3% in Australia and New Zealand to 32.7% in sub-Saharan Africa, with more developed countries having a lower rate of infection-related malignancies [2]. The carcinogenic potential of infections often has been attributed to their direct effects on the mechanisms of cancer initiation, development, and progression, or indirectly as a result of induced inflammatory or epigenetic alterations in the immune system. Several reports regarding the carcinogenic effects of bacterial [3-18], parasitic [19, 20], and fungal [21-28] organisms and their relation to human disorders and the development of cancer are available. While the widespread existence of mycoviruses in fungi is well recognized and their effects on various crops have been demonstrated [29-56], their direct effects on human health have not yet been fully investigated [53-56]. More extensive data regarding the connection of other viral agents and cancer are available [57, 58]. Advances

in epidemiology, infectious diseases, and molecular biology, have disclosed a significant amount of information relating to the potential of infections to produce cancer and mechanisms of their carcinogenic or leukemogenic effects [59-73]. Cancers that are assumed to be caused by infections are generally reported to have a higher mortality rate than other malignant disorders [2]. Among various organisms, viruses are most often suspected to contribute to the development of cancers [74-119]. The finding of viral gene products in some malignant cells that acquire anti-apoptotic phenotypes points to such involvement. Both DNA and RNA viruses are proposed to be involved in the process of carcinogenesis (Table-1).

Table 1: Examples of viruses implicated in human cancers.

Virus	Viral Taxonomy	Genome	Possible association with cancer
EBV	Herpesviridae	dsDNA 172 kb~90ORFs	BL, NPC, Lymphoma, HL
BKV	Polyomaviridae	dsDNA~5.2 kb	E, G, F, N, P, Li, O, Possible prostate
HBV	Hepadnaviridae	dsDNA 3.2 kb 4 ORFs	HCC
HCV	Flaviviridae	dsRNA 9.4 kb 9 ORFs	HCC, Lymphoma, GI, CR, ES, B
HERVs	Retroviridae	dsRNA/DNA?	Seminomas, breast, GC, KS, Le, melanoma, P
HIV	Retroviridae	dsRNA	KS, NHL, HL, Cervical, Anal, Conjunctiva
HMTV	Retrovir	dsRNA/DNA?	Breast carcinoma
HPV	Papillomaviridae	dsDNA 8 kb 8–10 ORFs	Oral, cervical, anogenital, Oropharynx, Tonsil
HTLV-1	Retroviridae	dsRNA 9.0 kb 6ORFs	Adult T-cell leukemia/lymphoma
JCV	Polyomaviridae	dsDNA ~ 5.2 kb	Possible medulloblastoma
KSHV	Herpesviridae	dsDNA 165 kb ~ 90ORFs	Kaposi sarcoma, primary effusion lymphoma
SV40	Polyomaviridae	dsDNA~5.2kb	B, O, malignant mesothelioma, lymphoma
TTV	Circoviridae	ssDNA 3.8 kb	Cervical, lung, possible head and neck

Reference: McLaughlin-Drubin, M. E., & Munger, K. (2008). Viruses associated with human cancer. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1782(3), 127-150.

Abbreviations: ATL: Adult T-cell leukemia; B: Brain; BKV: Burkitt's virus; BL: Burkitt's lymphoma; BKV: BK virus; CR: Colorectal; E: Ependymoma; EBV: Epstein–Barr virus; Es: Esophageal; HBV: Hepatitis B virus; F: Fibrosarcoma; HL: Hodgkin's lymphoma; G: Glioma; GC: Germ cell; GI: Gastrointestinal; HERVs: Human endogenous retroviruses; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HMTV: Human mammary tumor virus; HPV: Human papillomavirus; HTLV-1: Human T-cell leukemia virus; JCV: JC virus; KS: Kaposi's sarcoma; KSHV: Kaposi's sarcoma-associated herpesvirus; Le: leukemia; Li: Liposarcoma; NPC: Nasopharyngeal carcinoma; N: Neuroblastoma; NHL: Non-Hodgkin's lymphoma; O: Osteosarcoma; P: Pancreatic tumors; SV40: Simian virus 40; TTV: Torque teno virus.

This includes DNA viruses such as Epstein-Barr virus (EBV) [76-80], human papillomavirus (HPV) [81-89], human immunodeficiency virus (HIV) [86, 89, 108-114], human herpes virus-8 (HHV), [90-92] hepatitis B virus [98-101] and RNA viral agents such as Human T lymphotropic virus type 1(HTLV-1) [93-97] and hepatitis C virus [99, 102, 103]. Emerging data regarding molecular events underlying the tumorigenic potential of human oncoviruses reveals that virus-host interactions can also occur at the epigenetic level [3, 104]. Epigenetic alterations are stable long-term changes in the DNA, which are normal evolutionary biological processes, necessary for adaptations to the environment. These do not result in alteration of the DNA sequence but can affect genomic stability and gene expression. Interaction between viral proteins and the epigenetic system can potentially lead to alterations in the epigenetic organization of the cell leading to carcinogenesis. There is increasing evidence that oncogenic viruses can affect molecular events and contribute to the epigenetic changes which may be involved in this process. Certain viral agents can interfere with the host epigenetic structure resulting in aberrations of DNA methylation and changes in histone modifications. Epigenetic changes such as altered miRNA expression and alteration in DNA methylation can promote the expression of oncogenes and the silencing of tumor-suppressor genes. Since some miRNA genes may be regulated by epigenetic mechanisms, it has been postulated that alterations in the methylation state and deregulation of miRNA promoters have the potential to be

the motivator of aberrant expression in cervical cancer [104]. This may be the case in certain types of human papillomavirus infection. The DNA methylation pattern of viral and host genome, histone modification, and gene silencing by non-coding RNAs can result in initiation and maintenance of epigenetic changes, potentially leading to cervical carcinogenesis [104]. While in the past bacterial infections were not considered to be associated with the development of cancer, in recent years their involvement in carcinogenesis through induction of chronic inflammation and production of carcinogenic bacterial metabolites have been explored [4-18]. Moreover, recent studies have examined changes in the intestinal flora and microbial metabolites in colorectal cancer and their relation to the immune system and inflammatory abnormalities. An example of the inflammatory mechanism inducing carcinogenesis is Helicobacter pylori which are classified as a class I carcinogen by the World Health Organization [4, 7]. Epidemiologically this agent has been linked to the distal gastric adenocarcinoma by inducing cell proliferation and production of mutagenic free radicals and N-nitroso compounds [4-7]. Bacterial agents can also produce other metabolites suspected to be carcinogenic. This is best exemplified by their carcinogenic ability in colon cancer. Bile salt metabolites increase colonic cell proliferation. It is known that taurocholic acid is capable of stimulating intestinal bacteria which in turn convert taurine and cholic acid to hydrogen sulfide and deoxycholic acid, genotoxin, and promotor of tumors, respectively. Exogenous compounds such as rutin may be metabolized into mutagens [7, 8]. Similarly, in pancreatic cancer, some studies have suggested a link between bacteria, chronic infection, and risk of tumorigenesis [4, 10-15]. Growing evidence suggests that the development of pancreatic cancer can be due to factors ranging from inflammation and immune activation to increased nitrosamine exposure. A higher risk of pancreatic cancer in individuals with periodontitis, which is largely driven by keystone pathogens and pathobionts, as compared to controls, has been reported [16, 17]. Additionally, elevated levels of antibodies to Porphyromonas gingivalis in blood, before the diagnosis of pancreatic cancer have been found [14]. It is not clear if the reported relationship between bacteria and pancreatic cancer is cause and effect, reactivity, or both [4, 10-17]. In one study, the bacterial DNA profile in the pancreas was found to be similar to those of the duodenum of the same individual, which may suggest that bacteria may have migrated from the intestinal lumen to the pancreas [18].

Parasites such as Opisthorchis viverrine, and Schistosoma hematobium, parasitic flatworms, can cause cholangiocarcinoma and bladder cancer, respectively [19, 20]. The association between Schistosoma japonicum, Schistosoma mansoni, and hepatocellular carcinoma has been reported [20].

The relation of fungal organisms and cancer has long been suspected, and up until recently, often attributed to their mycotoxin production [21-27]. Immunosuppressive effects of fungal agents such as mycotoxin have been recognized as culprits related to different types of cancer [27]. Several mycotoxins are considered to be mutagenic and Aflatoxin B1, Ochratoxin A, and fumonisins are known to be potent carcinogens. For example, aflatoxins have been suspected to induce hepatocellular carcinoma, ochratoxin to cause cancer of the urinary tract, and fumonisins to induce esophageal cancer [21-27]. There is some evidence that Candida albicans increases the risk of carcinogenesis and metastasis by various mechanisms, including inducing inflammation, producing carcinogenic byproducts, induction of Th17 response, and molecular mimicry [28]. Viruses infecting fungi, known as mycoviruses, can affect fungal organisms [29, 30]. It is estimated that from 30 to 80% of all fungal species, predominantly endophytic fungi, may contain mycoviruses [30]. Mycoviruses in fungi can be transmitted intracellularly during cell division, sporogenesis, and cell fusion [31-34] and the presence of mycoviruses in various species has been well characterized [29, 34, 41]. The genome of most mycoviruses consists of double-stranded RNA (dsRNA), while in about 30% of mycoviruses this is composed of a positive, single-stranded RNA (+ssRNA) [33-37]. A geminivirus-related DNA mycovirus and the existence of multiple viruses in given fungi have been reported. While often cryptic or asymptomatic, infection of fungi with mycoviruses can lead to phenotypic changes in their host, resulting in perturbance of sporulation, disturbance of growth, hypovirulence, or hypervirulence in entomo- and phytopathogenic fungi. Such infestation can even be fatal to the host. Hypovirulence induced by mycoviruses in the fungal hosts has been used as a biological control mechanism, therefore, much research has focused on mycoviruses that infect economically important fungi [33-37].

Often, there is a state of genetic conflict between mycoviruses and their host. In general, fungi lack any known mechanisms of innate and adaptive immunity, however, they can utilize RNA degradation as an antiviral defense system [38-39]. In some strains of Aspergillus flavus such as NRRL 5565, the presence of mycovirus results in the suppression of aflatoxin production, and in Aspergillus Niger, reduced radial rate of growth. These phenomena have been used in agriculture to control the production of carcinogenic aflatoxins. Changes in pigmentation, growth rate, biomass, spore production, and RNA silencing may indicate the ability of mycoviruses to alter the genetics and function of their host [40-50]. As the transfer of the genetic content to a fungal host occurs by transformation and transfection, the effects of these transfers in humans exposed to mycovirus-infected fungi are not known and need to be explored.

Mycoviruses carrying dsRNA genome that can be pathogenic in humans have been classified as Partitiviridae, Totiviridae, Chrysoviridae, Reoviridae, and Hypoviridae [42]. While there has been significant interest and research on the effects of mycoviruses in agricultural domains, their possible effect solely, or in combination with their fungal host, on human health has not been

thoroughly investigated, and descriptions of such involvement are rarely published reiterating the unmet need for new studies. In one study, extrachromosomal dsRNA segments in clinical isolates of Malassezia species, which is the most common fungal infection of the human skin, were observed [53]. A novel dsRNA segment was identified, and the sequencing results revealed that the virus, named MrV40, belongs to the Totiviridae family. Comparison of the transcriptome of virus-infected Malassezia restricta cells to that of virus-cured cells revealed that transcripts involved in ribosomal biosynthesis were downregulated and those involved in energy production and programmed cell death were upregulated. Transmission electron microscopy had revealed significantly larger vacuoles in virus-infected Malassezia restricta cells. This was interpreted as an indication that MrV40 infection significantly alters Malassezia restricta's physiology [53]. The report also indicates that viral nucleic acid from MrV40 can induce a Toll-like receptor 3 (TLR3) mediated inflammatory immune response in bone marrow-derived dendritic cells, which suggests a viral element contributes to the pathogenicity of Malassezia [53]. The finding that in the infected cells expression of genes involved in ribosomal synthesis and programmed cell death was altered indicates that infection with mycovirus affects the physiology of the fungal host cells [53].

Most recently, a mycovirus containing Aspergillus flavus, isolated from the home of a patient with acute lymphoblastic leukemia was reported to reinduce genetic and cell surface phenotypes, characteristic of acute lymphoblastic leukemia, in the mononuclear leukocytes from patients with this disease in full remission, without any evidence of the disease, and long-term survivors when compared to negative controls [54]. In a related study, using enzyme-linked immunoassay (ELISA) test, plasma of patients with ALL had a positive immunological reaction, while three separate groups of controls, including healthy blood donors, patients with sickle cell disease, and those with a variety of solid tumors, were negative [55]. These findings may point to a role for the mycovirus containing Aspergillus flavus in leukemogenesis in acute lymphoblastic leukemia [31, 54-56].

Role of infections in carcinogenesis

For long, infections have been hypothesized to be, at least in part, causative factors for the development of cancer in general. Several infectious agents are reported to be carcinogenic or leukemogenic. The number of mechanisms by which each individual or group of infections can cause cancer, including leukemia, is diverse [57, 58], and generally uncertain. These include, but are not limited to, induction of genetic and epigenetic changes, impairment of the host immune system and response, instability due to chronic inflammation, changes in signals regarding the balance between proliferation and antiproliferation, and other mechanisms.

Some of the hypotheses offered for childhood cancers in general, and acute leukemias in particular, include "population-mixing" and genetic mutation with delayed infection [61-72]. While these hypotheses differ in detail and mechanism, they share common ground, since they postulate that childhood leukemia occurs as a result of a response to infections. More recently, a revised two-hit model for the development of B-cell ALL has been proposed [70]. The "two-hit theory" suggests that the first step, which involves a predisposing genetic mutation, namely fusion gene formation or hyperdiploidy and production of pre-leukemic clones, occurs in utero [70]. The second step, which is postulated to be exposed to infections to trigger the critical secondary cellular mutations, is suggested to happen later in life [70] based on this theory, infections early in life are protective, but in a small sub-population, a later exposure triggers the critical secondary cellular mutations which result in the development of ALL [70]. It is estimated that the first step occurs in approximately 5% of newborns, but only one in 100 of the predisposed will go on to go through the second step and develop the disease. No indication as to the nature of infections that trigger the second step in the process is provided [68-72]. In support of the combination of genetics and infections to trigger the development of ALL, experimental models are available [73]. In murine experimental studies, pre-B ALL was initiated in mice heterozygous for PAX (PAX5+/-) upon exposure to common pathogens. Historically, several infective agents including viral, bacterial, fungal, and parasitic agents have been proposed to cause a variety of other cancers. Of all infections, viruses have been more often reported to be associated with certain malignant disorders [74].

Interestingly, while mycoviruses are relatively common in fungi in the natural environment, only rare reports regarding their combination and possible involvement in carcinogenesis have been reported [31, 54-56].

In recent years, several DNA and RNA viruses are reported to be related to carcinogenesis [74-118] and among the most commonly attributed viruses have been Epstein-Barr virus, human papillomavirus, human herpes virus-8, Hepatitis B and C viruses, Human immunodeficiency virus, Human T-cell Lymphotropic Virus type 1, etc. These have been classified as type 1 carcinogenic agents by the International Agency for Research on Cancer (IARC). Carcinogenic effects of viruses often depend on additional factors such as genetic predisposition, various somatic mutations or immunosuppression of the host, or combination with exposure to chemical carcinogens.

Among herpesviruses associated with carcinogenesis, Epstein-Barr, a ubiquitous virus with large double-stranded DNA genomes, is the most investigated agent for its effect in the development of Burkitt's lymphoma [75-80]. EBV can infect B cells and epithelial cells and establish latency in B lymphocytes and reactivate the lytic cycle. The surface glycoprotein, BLLE1 (gp350/220), binds to the CD21 receptor located on the B cells. EBV directly enters the latent gene expression state, resulting in the suppression

of the lytic cycle. While commonly known as an agent for the development of infectious mononucleosis, EBV is associated with several malignant disorders, such as nasopharyngeal carcinomas, B and T cell lymphomas, post-transplant lymphoproliferative disease, Hodgkin's lymphoma, and leiomyosarcomas [75-80]. Individuals with decreased immunity and immune surveillance appear to be more prone to the malignant transformations caused by EBV. Malaria, which is common in the central part of Africa, may be a cofactor in the carcinogenesis of EBV [79].

Human papillomavirus that infects epithelial cells is reported to be associated with the development of cervical cancer, the second leading cause of mortality due to malignancy in women [82, 83]. It also may play a role in the development of head and neck tumors, cutaneous and anogenital cancers [81-84]. Co-factors such as use of hormonal contraceptives, tobacco smoking, high parity, HIV, Chlamydia trachomatis (CT), and herpes simplex virus type-2 (HSV-2) infections, immunosuppression, inadequate T cell response, and some dietary deficiencies may also be involved in this process. HPV has also been associated with penis, anus, vagina, vulva, mouth, and throat cancers [85-89].

Human herpesvirus-8 (HHV-8), also known as Kaposi sarcoma-associated herpesvirus (KSHV), predominantly infects B lymphocyte [90]. It encodes latency-associated nuclear antigen (LANA) and is expressed in the Kaposi sarcoma, Castleman's disease, and primary effusion lymphoma (PEL) cells [90, 91]. This may suggest that LANA plays a role in the pathogenesis of HHV-8–associated cancers. It is demonstrated that the viral genome is expressed in these malignant disorders and encodes transforming proteins and anti-apoptotic factors. Kaposi sarcoma is one of the most common malignancies seen in HIV-infected patients [86, 89]. Studies have shown that HHV-8 tumorigenesis is mediated through molecular mimicry, hence viral-encoded proteins can potentially activate several cellular signaling cascades while evading immune surveillance. The development of Kaposi sarcoma is most common in individuals with immune depression and is the second most frequent tumor in acquired immune deficiency syndrome patients [93].

Human T-cell Leukaemia/Lymphotropic virus type 1 (HTLV-1) is a single-stranded RNA retrovirus that is known to be associated with adult T-cell leukemia/lymphoma. HTLVs are classified as the Delta-retroviruses genera of the Orthoretrovirinae subfamily [93-95]. Mechanisms of action of HTLV-1 in the development of adult T cell leukemia are not well understood. It is postulated that the HTLV-1 viral transactivator/oncoprotein, Tax, activate viral transcription and seizes the regulatory mechanism [96, 97]. This plays a role in the process through the activation of viral transcription and the hijacking of cellular growth and cell division. There is evidence, however, that HTLV-1 infection may not by itself be sufficient to cause this transformation. Some findings suggest that the reduced diversity, frequency, and function of HTLV-1 specific CD8+ T cells of the host may play a role in the development of adult T-cell leukemia. There is a significant latency, which can be many years after HTLV-1 infection and the development of T-cell leukemia. HTLV-1 viral transactivator/oncoprotein Tax, which is a regulatory protein capable of viral replication and T-cell transformation, is suspected to be involved in the progression from clinical latency to the development of T-cell leukemia [96, 97].

Hepatitis B virus (HBV), a DNA virus of hepadnaviridae family, and hepatitis C, an enveloped RNA virus of the flavivirus family, are found to be associated with carcinogenesis in certain populations [97-103]. Epidemiological studies reveal a role for these viral agents in hepatocellular carcinogenesis. Coinfection with both viruses appears to carry a synergistic risk for the development of this disorder. Hepatitis C virus is an enveloped RNA virus that is capable of causing acute and chronic hepatitis. Chronic infection with the hepatitis C virus can result in the development of cirrhosis, which in turn, in a small sub-population, can lead to hepatocellular carcinoma [102, 103].

To date, Merkel cell polyomavirus (MCPV) is the only polyomavirus that is associated with human cancer in the immunocompromised population [105-107]. This virus contributes to the development of Merkel cell carcinoma (MCC).

Individuals infected by the human immunodeficiency virus are found to have an increased risk of developing certain cancers, including Kaposi sarcoma and non-Hodgkin lymphoma [109-114]. The acquired immunodeficiency syndrome (AIDS) caused by HIV, results in the progressive depletion of CD4+T lymphocytes, resulting in the deficiency of cell-mediated immune system. Patients with AIDS are at risk for high-grade immunoblastic lymphoma, low-grade lymphoma, and central nervous system lymphoma. Liver, lung, breast, cervical carcinoma, anal and other cancers have also been found with more frequency in adult patients with HIV and regarding the liver malignancy, in those who are co-infected with both HBV and HIV in certain endemic areas [109-114].

The carcinogenesis of some other viruses such as Simian Virus 40 (SV40) is not certain. SV40 was suggested, but not always proven, to increase the risk of developing mesothelioma, lymphomas, brain and bone cancers [115-118].

Mycoviruses

Mycoviruses are widespread worldwide, infect fungi, and in several ways can alter the normal function of their host, including alterations on fungal phenotype, affecting mycotoxin production, morphology, pigmentation, asexual and sexual sporulation, and growth. Mycoviral infection is persistent and normally does not result in the demise of the host. Fungi can be infected with two or more unrelated mycoviruses. Most mycoviruses have double-stranded RNA (ds RNA) genomes, however, approximately 30%

have positive-sense, single-stranded RNA (+ssRNA) genomes, with one family having a circular ssDNA genome. Currently, the International Committee on Taxonomy of Viruses has classified mycoviruses into 22 taxa (21 families and one genus). Some mycoviruses have a close relation to known human pathogens. For example, the family Mymonaviridae belongs to the order Mononegavirales, along with Ebola, measles, mumps, Nipah, rabies, and human respiratory syncytial virus. Families Metaviridae and Pseudoviridae belong to the order Ortervirales, which also includes human immunodeficiency virus and retroviruses.

Even though mycoviruses have global distribution affecting fungi including those with which humans come in contact frequently, their possible role on health is poorly investigated. Most investigations of the effects of mycoviruses have concentrated on using those which have transmissible hypovirulence as a biocontrol method for control of crop-related fungal infestation [31, 120, 121]. On the opposite side, hypervirulence induced by mycoviruses resulting in increased fungal pathogenicity can also occur. These changes point to the importance of mycoviruses and their ability in changing the fungal phenotype, which potentially can affect their pathogenicity. The combination of mycovirus and fungus appears to create an organism that biologically is significantly different from the usual host. Some medical studies have concentrated on the possible use of mycoviruses as future therapeutic agents for the biological control of pathological invasive fungi [121].

As noted, based on serological and cellular studies it is hypothesized a possible role for a mycovirus infected Aspergillus flavus in the leukemogenesis of B-cell acute lymphoblastic leukemia. These investigations may indicate that mycovirus containing Aspergillus flavus may have a part in the mechanism of leukemogenesis in ALL. Furthermore, it provides a constant infectious agent for the so-called two-hit theories combining a genetic mutation and an infection for the genesis of ALL [56, 70]. The findings ultimately have the possibility of producing a test for identifying those who have the potential for the development of ALL, a diagnostic test for this disease, and a vaccine to prevent it [122, 123]. The possible role of mycovirus containing fungal agents in carcinogenesis, in general, needs further investigation.

Summary

Some infection organisms appear to have an integral role in certain carcinogenic events. These include members of viral, bacterial, and parasitic groups. In particular, viruses appear to induce diverse biological pathways to carcinogenesis, evidenced by the presence of the viral gene products in some cancers and precancerous cells. For example, in malignancies such as cervical carcinoma, the DNA specific to the human papillomavirus appears to integrate into the host cell genome, and viral oncoproteins E6 and E7 consequently disrupt natural tumor suppressor pathways which culminates in the proliferation of cervical carcinoma cells. Recent findings revealing that the plasma of patients with ALL immunologically react to the products of a mycovirus containing Aspergillus flavus is of interest and represents the presence of factors that can be used for clinical interventions. Furthermore, exposure of mononuclear leukocytes of these patients to the products of the above-mentioned organism was found to reproduce genetic and phenotypic characteristics of ALL, which is of great significance. This may provide a constant infectious agent for the so-called two-hit theory. Mycoviruses are reported to be able to significantly alter the biological characteristics of their host. The possible role of mycoviruses, with and without their fungal host, has been poorly investigated in human diseases in general, and cancer and leukemia in particular, and this unmet need must be addressed.

Author's Contribution

Cameron K. Tebbi, M.D. has researched, prepared, and written the manuscript.

Conflict of Interest

The author has no conflict of interest.

Personal Financial Interest

The author has no personal financial interest regarding publication of this article.

Non-financial Competing Interest

The author has no non-financial competing interest or personal relationships that could have influenced the work reported in this paper.

Overlapping Publication

This article has not been submitted to any other journal for publication.

Confidentiality and Anonymity

This article does not contain the name, identity, information or address of any patient or individual, except for the author.

Author Statement

This manuscript has been read and approved by the author. The author meets requirements for authorship and the manuscript is written by him.

Ethics

This manuscript in in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The review presented meets the recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals regarding human populations including sex, age and ethnicity.

References

1. Ahmed HG (2012) Awareness survey on knowledge of microbial infectious causes of cancer in northern state of Sudan. Asian Pac J Cancer Prev 13: 5497-5500. https://doi.org/10.7314/apjcp.2012.13.11.5497
2. De Martel C, Ferlay J, Franceschi S, et al. (2012) Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol 13: 607-615. https://doi.org/10.1016/S1470-2045(12)70137-7
3. Latvala A, Ollikainen M (2016) Mendelian randomization in (epi)genetic epidemiology: an effective tool to be handled with care. Genome Biol 17: 156. https://doi.org/10.1186/s13059-016-1018-9
4. Michaud DS (2013) Role of bacterial infections in pancreatic cancer. Carcinogenesis 34: 2193-2197. https://doi.org/10.1093/carcin/bgt249
5. Sonnenberg A, Genta RM (2013) Helicobacter pylori is a risk factor for colonic neoplasms. Am J Gastroenterol 108: 208-215. https://doi.org/10.1038/ajg.2012.407
6. Chmiela M, Karwowska Z, Gonciarz W, et al. (2017) Host pathogen interactions in Helicobacter pylori related gastric cancer. World J Gastroenterol 23: 1521-1540. https://dx.doi.org/10.3748%2Fwjg.v23.i9.1521
7. Touati E (2010) When bacteria become mutagenic and carcinogenic: lessons from H. pylori. Mutat Res 703: 66-70. https://doi.org/10.1016/j.mrgentox.2010.07.014
8. Laires A, Pacheco P, Rueff J (1989) Mutagenicity of rutin and the glycosidic activity of cultured cell-free microbial preparations of human faeces and saliva. Food Chem Toxicol 27: 437-443. https://doi.org/10.1016/0278-6915(89)90029-X
9. Kim DH, Jung EA, Sohng IS, et al. (1998) Intestinal bacterial metabolism of flavonoids and its relation to some biological activities. Arch Pharm Res 21: 17-23. https://doi.org/10.1007/BF03216747
10. Li P, Shu Y, Gu Y (2020) The potential role of bacteria in pancreatic cancer: a systematic review. Carcinogenesis 41: 397-404. https://doi.org/10.1093/carcin/bgaa013
11. Swidsinski A, Schlien P, Pernthaler A, et al. (2005) Bacterial biofilm within diseased pancreatic and biliary tracts. Gut 54: 388-395. https://doi.org/10.1136/gut.2004.048900
12. Morgell A, Reisz JA, Ateeb Z, et al. (2021) Metabolic characterization of plasma and cyst fluid from cystic precursors to pancreatic cancer patients reveal metabolic signatures of bacterial infection. J Proteome Res 20: 2725-2738. https://doi.org/10.1021/acs.jproteome.1c00018
13. Hajishengallis G (2014) Immunomicrobial pathogenesis of periodontitis: keystones, pathobionts, and host response. Trends in immunol 35: 3-11. https://doi.org/10.1016/j.it.2013.09.001
14. Michaud DS, Izard J, Wilhelm-Benartzi CS, et al. (2013) Plasma antibodies to oral bacteria and risk of pancreatic cancer in a large European prospective cohort study. Gut 62: 1764-1770. https://doi.org/10.1136/gutjnl-2012-303006
15. Schneider J, Schenk P, Obermeier A, et al. (2015) Microbial colonization of pancreatic duct stents: a prospective analysis. Pancreas 44: 786-790. https://doi.org/10.1097/MPA.0000000000000332
16. Michaud DS, Fu Z, Shi J, et al. (2017) Periodontal disease, tooth loss, and cancer risk. Epidemiol Rev 39: 49-58. https://doi.org/10.1093/epirev/mxx006
17. Fan X, Alekseyenko AV, Wu J, et al. (2018) Human oral microbiome and prospective risk for pancreatic cancer: a population-based nested case-control study. Gut 67: 120-127. https://doi.org/10.1136/gutjnl-2016-312580
18. Del Castillo E, Meier R, Chung M, et al. (2019) The microbiomes of pancreatic and duodenum tissue overlap and are highly subject specific but differ between pancreatic cancer and noncancer subjects. Cancer Epidemiol Biomarkers Prev 28: 370-383. https://doi.org/10.1158/1055-9965.EPI-18-0542
19. Khurana S, Dubey ML, Malla N (2005) Association of parasitic infections and cancers. Indian J Med Microbiol 23: 74-79. https://doi.org/10.1016/S0255-0857(21)02644-X
20. Abdel-Rahim AY (2001) Parasitic infections and hepatic neoplasia. Dig Dis 19: 288-291. https://doi.org/10.1159/000050695
21. Magnussen A, Parsi MA (2013) Aflatoxins, hepatocellular carcinoma and public health. World J Gastroenterol 19: 1508-1512. https://doi.org/10.3748/wjg.v19.i10.1508
22. Kew MC (2013) Aflatoxins as a cause of hepatocellular carcinoma. J Gastrointestin Liver Dis 22: 305-310.
23. Kanhayuwa L, Kotta-Loizou I, Özkan S, et al. (2015) A novel mycovirus from aspergillus fumigatus contains four unique dsRNAs as its genome and is infectious as dsRNA. Proc Natl Acad Sci U S A 112: 9100-9105. https://doi.org/10.1073/pnas.1419225112
24. Clark HA, Snedeker SM (2006) Ochratoxin a: its cancer risk and potential for exposure. J Toxicol Environ Health B Crit Rev 9: 265-296. https://doi.org/10.1080/15287390500195570
25. Bui-Klimke TR, Wu F (2015) Ochratoxin A and human health risk: a review of the evidence. Crit Rev Food Sci Nutr 55: 1860-1869. https://doi.org/10.1080/15287390500195570
26. Teixeira HC, Calich VL, Singer-Vermes LM (1987) Experimental

paracoccidioidomycosis: early immunosuppression occurs in susceptible mice after infection with pathogenic fungi. Braz J Med Biol Res 20: 587-589.

27. Pitt JI (2000) Toxigenic fungi: which are important? Med Mycol 38 Suppl 1: 17-22.

28. Ramirez-Garcia A, Rementeria A, Aguirre-Urizar JM, et al. (2016) Candida albicans and cancer: Can this yeast induce cancer development or progression? Crit Rev Microbiol 42: 181-193. https://doi.org/10.3109/1040841X.2014.913004

29. Ellis LF, Kleinschmidt WJ (1967) Virus-like particles of a fraction of statolon, a mould product. Nature 215: 649-650. https://doi.org/10.1038/215649a0

30. Ghabrial SA, Castón JR, Jiang D, et al. (2015) 50-plus years of fungal viruses. Virology 479-480: 356-368. https://doi.org/10.1016/j.virol.2015.02.034

31. Tebbi CK, Kotta-Loizou I, Coutts RH (2021) Mycovirus containing aspergillus flavus and acute lymphoblastic leukemia. Carcinogenesis beyond mycotoxin production. Intech open book series. The Genus Aspergillus - Pathogenicity, Mycotoxin Production and Industrial Applications. https://doi.org/10.5772/intechopen.98897

32. Siddique AB (2020) Viruses of endophytic and pathogenic forest fungi. Virus Genes 56: 407-416. https://doi.org/10.1007/s11262-020-01763-3

33. Xie J, Jiang D (2014) New insights into mycoviruses and exploration for the biological control of crop fungal diseases. Annu Rev Phytopathol 52: 45-68. https://doi.org/10.1146/annurev-phyto-102313-050222

34. Nuss DL (2005) Hypovirulence: mycoviruses at the fungal-plant interface. Nat Rev Microbiol 3: 632-642. https://doi.org/10.1038/nrmicro1206

35. Sukphopetch P, Suwanmanee S, Pumeesat P, et al. (2021) In vitro characterization of chrysovirus-1-induced hypovirulence of bipolaris maydis. Walailak J Sci Technol 18: 6564-6568. https://doi.org/10.48048/wjst.2021.6564

36. Kotta-Loizou I, Coutts RH (2017) Studies on the virome of the entomopathogenic fungus beauveria bassiana reveal novel dsrna elements and mild hypervirulence. PLoS Pathog 13: e1006183. https://doi.org/10.1371/journal.ppat.1006183

37. Filippou C, Diss RM, Daudu JO, et al. (2021) The polymycovirus-mediated growth enhancement of the entomopathogenic fungus beauveria bassiana is dependent on carbon and nitrogen metabolism. Front Microbiol 12: 606366. https://doi.org/10.3389/fmicb.2021.606366

38. Rowley PA, Ho B, Bushong S, et al. (2016) XRN1 is a species-specific virus restriction factor in yeasts. PLoS Pathog 12: e1005890. https://doi.org/10.1371/journal.ppat.1006002

39. Bormann J, Heinze C, Blum C, et al. (2018) Expression of a structural protein of the mycovirus FgV-ch9 negatively affects the transcript level of a novel symptom alleviation factor and causes virus infection-like symptoms in fusarium graminearum. J Virol 92: e002678. https://doi.org/10.1128/JVI.00326-18

40. van Diepeningen AD, Debets AJ, Hoekstra RF (2006) Dynamics of dsRNA mycoviruses in black Aspergillus populations. Fungal Genet Biol 43: 446-452. https://doi.org/10.1016/j.fgb.2006.01.014

41. Bhatti MF, Bignell EM, Coutts RH (2011) Complete nucleotide sequences of two dsRNAs associated with a new partitivirus infecting Aspergillus fumigatus. Arch Virol 156: 1677-1680. https://doi.org/10.1007/s00705-011-1045-5

42. Keceli SA (2017) Mycoviruses and importance in mycology. Mikrobiyol Bul 51: 404-412. https://doi.org/10.5578/mb.54128

43. Ozkan S, Coutts RH (2015) Aspergillus fumigatus mycovirus causes mild hypervirulent effect on pathogenicity when tested on Galleria mellonella. Fungal Genet Biol 76: 20-26. https://doi.org/10.1016/j.fgb.2015.01.003

44. Son M, Yu J, Kim KH (2015) Five Questions about Mycoviruses. PLoS Pathog 11: e1005172. https://doi.org/10.1371/journal.ppat.1005172

45. Abbas A (2016) A review paper on mycoviruses. J Plant Pathol Microbiol 7: 390.

46. Cho WK, Lee KM, Yu J, et al. (2013) Insight into mycoviruses infecting Fusarium species. Adv Virus Res 86: 273-288. https://doi.org/10.1016/b978-0-12-394315-6.00010-6

47. Mochama P, Jadhav P, Neupane A, et al. (2018) Mycoviruses as triggers and targets of RNA silencing in white mold fungus sclerotinia sclerotiorum. Viruses 10: 214. https://doi.org/10.3390/v10040214

48. Yu J, Kim KH (2020) Exploration of the interactions between mycoviruses and fusarium graminearum. Adv Virus Res 106: 123-144. https://doi.org/10.1016/bs.aivir.2020.01.004

49. Lee KM, Yu J, Son M, et al. (2011) Transmission of fusarium boothii mycovirus via protoplast fusion causes hypovirulence in other phytopathogenic fungi. PLoS One 6: e21629. https://doi.org/10.1371/journal.pone.0021629

50. Lee KM, Cho WK, Yu J, et al. (2014) A comparison of transcriptional patterns and mycological phenotypes following infection of fusarium graminearum by four mycoviruses. PLoS One 9: e100989. https://doi.org/10.1371/journal.pone.0100989

51. Segers GC, Zhang X, Deng F, et al. (2007) Evidence that RNA silencing functions as an antiviral defense mechanism

in fungi. Proc Natl Acad Sci U S A 104: 12902-6. https://doi.org/10.1073/pnas.0702500104

52. Chu YM, Jeon JJ, Yea SJ, et al. (2002) Double-stranded RNA mycovirus from fusarium graminearum. Appl Environ Microbiol 68: 2529-2534. https://doi.org/10.1128/AEM.68.5.2529-2534.2002

53. Park M, Cho YJ, Kim D, et al. (2020) A novel virus alters gene expression and vacuolar morphology in malassezia cells and induces a tlr3-mediated inflammatory immune response. mBio 11:e01521-20. https://doi.org/10.1128/mbio.01521-20

54. Tebbi CK, Badiga A, Sahakian E, et al. (2021) Exposure to a mycovirus containing Aspergillus Flavus reproduces acute lymphoblastic leukemia cell surface and genetic markers in cells from patients in remission and not controls. Cancer Treat Res Commun 26: 100279. https://doi.org/10.1016/j.ctarc.2020.100279

55. Tebbi CK, Badiga A, Sahakian E, et al. (2020) Plasma of acute lymphoblastic leukemia patients react to the culture of a mycovirus containing aspergillus flavus. J Pediatr Hematol Oncol 42: 350-358. https://doi.org/10.1097/mph.0000000000001845

56. Tebbi CK (2021) Etiology of acute leukemia: a review. Cancers (Basel) 13: 2256. https://doi.org/10.3390/cancers13092256

57. Hausen HZ (2001) Proliferation-inducing viruses in non-permissive systems as possible causes of human cancers. Lancet 357: 381-384. https://doi.org/10.1016/s0140-6736(00)03652-7

58. Hausen HZ (2008) Infections causing human cancer. Yale J Biol Med 81: 52-53

59. Ward G (1917) The infective theory of acute leukaemia. Br J Child Dis 14: 10-20.

60. Da Silva MLR, De Albuquerque BHDR, Allyrio TADMF, et al. (2021) The role of HPV induced epigenetic changes in cervical carcinogenesis. Biomed Rep 15: 60. https://doi.org/10.3892/br.2021.1436

61. Law GR, Parslow RC, Roman E, et al. (2003) Childhood cancer and population mixing. Am J Epidemiol 158: 328-336. https://doi.org/10.1093/aje/kwg165

62. Law GR, Feltbowe RG, Taylor JC, et al. (2008) What do epidemiologists mean by 'population mixing'? Pediatr Blood Cancer 51: 155-160. https://doi.org/10.1002/pbc.21570

63. Kinlen LJ (2012) An examination, with a meta-analysis, of studies of childhood leukaemia in relation to population mixing. Br J Cancer 107: 1163-1168. https://doi.org/10.1038/bjc.2012.402

64. Stiller CA, Kroll ME, Boyle PJ, et al. (2008) Population mixing, socioeconomic status and incidence of childhood acute lymphoblastic leukaemia in England and Wales: analysis by census ward. Br J Cancer 98: 1006-1011. https://doi.org/10.1038/sj.bjc.6604237

65. Tucker MA (2004) Re: "Childhood cancer and population mixing". Am J Epidemiol 159: 716-717; author reply 717. https://doi.org/10.1093/aje/kwh098

66. Parslow RC, Law GR, Feltbower R, et al. (2002) Population mixing, childhood leukaemia, CNS tumours and other childhood cancers in Yorkshire. Eur J Cancer 38: 2033-2040. https://doi.org/10.1016/S0959-8049(02)00316-7

67. Greaves MF (1997) Aetiology of acute leukaemia. Lancet 349: 344-349. https://doi.org/10.1016/S0140-6736(96)09412-3

68. Kinlen L (1988) Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain. Lancet 2: 1323-1327. https://doi.org/10.1016/s0140-6736(88)90867-7

69. Greaves MF (1988) Speculations on the cause of childhood acute lymphoblastic leukemia. Leukemia 2: 120-125.

70. Greaves M (2018) A causal mechanism for childhood acute lymphoblastic leukaemia. Nat Rev Cancer 18: 471-484. https://doi.org/10.1038/s41568-018-0015-6

71. Greaves MF, Alexander FE (1993) An infectious etiology for common acute lymphoblastic leukemia in childhood? Leukemia 7: 349-360.

72. Greaves MF, Maia AT, Wiemels JL, et al. (2003) Leukemia in twins: lessons in natural history. Blood 102: 2321-2333. https://doi.org/10.1182/blood-2002-12-3817

73. Martin-Lorenzo A, Hauer J, Vicente-Duenas C, et al. (2015) Infection exposure is a causal factor in B-cell precursor acute lymphoblastic leukemia as a result of Pax5-inherited susceptibility. Cancer Discov 5: 1328-1343. https://doi.org/10.1158/2159-8290.cd-15-0892

74. Hausen HZ (1991) Viruses in human cancers. Science 254: 1167–1173. https://doi.org/10.1126/science.1659743

75. Hausen HZ, Schulte-Holthausen H, Klein G, et al. (1970) EBV DNA in biopsies of Burkitt tumours and anaplastic carcinomas of the nasopharynx. Nature 228: 1056-1058. https://doi.org/10.1038/2281056a0

76. McLaughlin-Drubin ME, Munger K (2008) Viruses associated with human cancer. Biochim Biophys Acta 1782: 127-150. https://doi.org/10.1016/j.bbadis.2007.12.005

77. Magrath I, Jain V, Bhatia K (1992) Epstein-Barr virus and Burkitt's lymphoma. Semin Cancer Biol 3: 285-295.

78. Shah KM, Young LS (2009) Epstein-Barr virus and carcinogenesis: beyond Burkitt's lymphoma. Clin Microbiol Infect 15: 982-988. https://doi.org/10.1111/j.1469-

0691.2009.03033.x

79. Donati D, Espmark E, Kironde F, et al. (2006) Clearance of circulating Epstein-Barr virus DNA in children with acute malaria after antimalaria treatment. J Infect Dis 193: 971-977. https://doi.org/10.1086/500839

80. Ho J (1978) An epidemiologic and clinical study of nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 4: 182-198.

81. Doeberitz MvK, Oltersdorf T, Schwarz E, et al. (1988) Correlation of modified human papilloma virus early gene expression with altered growth properties in C4-1 cervical carcinoma cells. Cancer Res 48: 3780-3786.

82. Li L, Xu C, Long J, et al. (2015) E6 and E7 gene silencing results in decreased methylation of tumor suppressor genes and induces phenotype transformation of human cervical carcinoma cell lines. Oncotarget 6: 23930-23943. https://doi.org/10.18632/oncotarget.4525

83. Stanley MA, Pett MR, Coleman N (2007) HPV: from infection to cancer. Biochem Soc Trans 35: 1456-1460. https://doi.org/10.1042/bst0351456

84. Jin J (2018) HPV infection and cancer. JAMA 319: 1058. https://doi.org/10.1001/jama.2018.0687

85. Muñoz N, Castellsagué X, de González AB, et al. (2006) HPV in the etiology of human cancer. Vaccine 24: S1-S10. https://doi.org/10.1016/j.vaccine.2006.05.115

86. Palefsky JM, Holly EA (2003) Chapter 6: immunosuppression and co-infection with HIV. J Natl Cancer Inst Monogr 2003: 41-46. https://doi.org/10.1093/oxfordjournals.jncimonographs.a003481

87. Halpert R, Fruchter RG, Sedlis A, et al. (1986) Human papillomavirus and lower genital neoplasia in renal transplant patients. Obstet Gynecol 68: 251-258.

88. Petry KU, Scheffel D, Bode U, et al. (1994) Cellular immunodeficiency enhances the progression of human papillomavirus-associated cervical lesions. Int J Cancer 57: 836-840. https://doi.org/10.1002/ijc.2910570612

89. Frisch M, Biggar RJ, Goedert JJ (2000) Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. J Natl Cancer Inst 92: 1500-1510. https://doi.org/10.1093/jnci/92.18.1500

90. Katano H, Sato Y, Sata T (2001) Expression of p53 and human herpesvirus-8 (HHV-8)-encoded latency-associated nuclear antigen with inhibition of apoptosis in HHV-8-associated malignancies. Cancer 92: 3076-3084.https://doi.org/10.1002/1097-0142(20011215)92:12<3076::AID-CNCR10117>3.0.CO;2-D

91. Sunil M, Reid E, Lechowicz MJ (2010) Update on HHV-8-associated malignancies. Curr Infect Dis Rep 12: 147-154. https://doi.org/10.1007/s11908-010-0092-5

92. Dwyer J, Le Guelte A, Galan Moya EM, et al. (2011) Remodeling of VE-cadherin junctions by the human herpes virus 8 G-protein coupled receptor. Oncogene 30: 190-200. https://doi.org/10.1038/onc.2010.411

93. Zhang LL, Wei JY, Wang L, et al. (2017) Human T-cell lymphotropic virus type 1 and its oncogenesis. Acta Pharmacol Sin 38: 1093-1103. https://doi.org/10.1038/aps.2017.17

94. Matsumoto S, Yamasaki K, Tsuji K, et al. (2008) Human T lymphotropic virus type 1 infection and gastric cancer development in Japan. J Infect Dis 198: 10-15. https://doi.org/10.1086/588733

95. Liu B, Liang MH, Kuo YL, et al. (2003) Human T-lymphotropic virus type 1 oncoprotein tax promotes unscheduled degradation of Pds1p/securin and Clb2p/cyclin B1 and causes chromosomal instability. Mol Cell Biol 23: 5269-5281. https://doi.org/10.1128/mcb.23.15.5269-5281.2003

96. Duggan DB, Ehrlich GD, Davey FP, et al. (1988) HTLV-I-induced lymphoma mimicking Hodgkin's disease. Diagnosis by polymerase chain reaction amplification of specific HTLV-I sequences in tumor DNA. Blood 71: 1027-1032.

97. Kozako T, Arima N, Toji S, et al. (2006) Reduced frequency, diversity, and function of human T cell leukemia virus type 1-specific CD8+ T cell in adult T cell leukemia patients. J Immunol 177: 5718-5726. https://doi.org/10.4049/jimmunol.177.8.5718

98. Beasley RP (1988) Hepatitis B virus. The major etiology of hepatocellular carcinoma. Cancer 61: 1942-1956. https://doi.org/10.1002/1097-0142(19880515)61:10<1942::AID-CNCR2820611003>3.0.CO;2-J

99. Perz JF, Armstrong GL, Farrington LA, et al. (2006) The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 45: 529-538. https://doi.org/10.1016/j.jhep.2006.05.013

100. Hoofnagle JH, Dusheiko GM, Schafer DF, et al. (1982) Reactivation of chronic hepatitis B virus infection by cancer chemotherapy. Ann Intern Med 96: 447-449.https://doi.org/10.7326/0003-4819-96-4-447

101. Chan SL, Wong VW, Qin S, et al. (2016) Infection and cancer: the case of hepatitis B. J Clin Oncol 34: 83-90. https://doi.org/10.1200/jco.2015.61.5724

102. Fattovich G, Giustina G, Degos F, et al. (1997) Morbidity and

mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 112: 463-472.

103. Yamamoto S, Kubo S, Hai S, et al. (2004) Hepatitis C virus infection as a likely etiology of intrahepatic cholangiocarcinoma. Cancer Sci 95: 592-595. https://doi.org/10.1111/j.1349-7006.2004.tb02492.x

104. Jiménez-Wences H, Peralta-Zaragoza O, Fernández-Tilapa G (2014) Human papilloma virus, DNA methylation and microRNA expression in cervical cancer. Oncol Rep 31: 2467-2476. https://doi.org/10.3892/or.2014.3142

105. Pietropaolo V, Prezioso C, Moens U. (2020) Merkel cell polyomavirus and merkel cell carcinoma. Cancers (Basel) 12: 1174. https://doi.org/10.3390/cancers12071774

106. Lipson EJ, Vincent JG, Loyo M, et al. (2013) PD-L1 expression in the Merkel cell carcinoma microenvironment: association with inflammation, Merkel cell polyomavirus and overall survival. Cancer Immunol Res 1: 54-63. https://doi.org/10.1158/2326-6066.cir-13-0034

107. Garneski KM, Warcola AH, Feng Q, et al. (2009) Merkel cell polyomavirus is more frequently present in North American than Australian Merkel cell carcinoma tumors. J Invest Dermatol 129: 246-248. https://doi.org/10.1038/jid.2008.229

108. Cote TR, Biggar RJ, Rosenberg PS, et al. (1997) Non-Hodgkin's lymphoma among people with AIDS: incidence, presentation and public health burden. AIDS/Cancer Study Group. Int J Cancer 73: 645-650. https://doi.org/10.1002/(SICI)1097-0215(19971127)73:5%3C645::AID-IJC6%3E3.0.CO;2-X

109. Cote TR, Manns A, Hardy CR, et al. (1996) Epidemiology of brain lymphoma among people with or without acquired immunodeficiency syndrome. AIDS/Cancer Study Group. J Natl Cancer Inst 88: 675-679. https://doi.org/10.1093/jnci/88.10.675

110. Otedo A, Simbiri KO, Were V, et al. (2018) Risk factors for liver Cancer in HIV endemic areas of Western Kenya. Infect Agent Cancer 13: 41. https://doi.org/10.1186/s13027-018-0214-5

111. Wallace SV, Carlin EM (2001) HIV in cervical cancer. Int J STD AIDS 12: 283-285.

112. Cadranel J, Garfield D, Lavole A, et al. (2006) Lung cancer in HIV infected patients: facts, questions and challenges. Thorax 61: 1000-1008. http://dx.doi.org/10.1136/thx.2005.052373

113. Cubasch H, Joffe M, Hanisch R, et al (2013) Breast cancer characteristics and HIV among 1,092 women in soweto, South Africa. Breast Cancer Res Treat 140: 177-186. https://doi.org/10.1007/s10549-013-2606-y

114. Dandapani SV, Eaton M, Thomas CR Jr, et al. (2010) HIV- positive anal cancer: an update for the clinician. J Gastrointest Oncol 1: 34-44. https://doi.org/10.3978/j.issn.2078-6891.2010.005

115. Shivapurkar N, Harada K, Reddy J, et al. (2002) Presence of simian virus 40 DNA sequences in human lymphomas. Lancet 35: 851-852. https://doi.org/10.1016/s0140-6736(02)07921-7

116. Atkin SJ, Griffin BE, Dilworth SM. (2009) Polyoma virus and simian virus 40 as cancer models: history and perspectives. Semin Cancer Biol 19: 211-217. https://doi.org/10.1016/j.semcancer.2009.03.001

117. Vilchez RA, Kozinetz CA, Arrington AS, et al. (2003) Simian virus 40 in human cancers. Am J Med 114: 675-684. https://doi.org/10.1016/s0002-9343(03)00087-1

118. Qi F, Carbone M, Yang H, et al. (2011) Simian virus 40 transformation, malignant mesothelioma and brain tumors. Expert Rev Respir Med 5: 683-697. https://dx.doi.org/10.1586%2Fers.11.51

119. Adams MJ, Lefkowitz EJ, King AM, et al. (2016) Ratification vote on taxonomic proposals to the International Committee on Taxonomy of Viruses Arch Virol 161: 2921-2949. https://doi.org/10.1007/s00705-016-2977-6

120. Kumar V, Chandel S (2016) Mycoviruses and their role in biological control of plant diseases. Int J Plant Sci 11: 375-382. https://doi.org/10.15740/HAS/IJPS/11.2/375-382

121. Van de Sande W, Lo-Ten-Foe JR, van Belkum A, et al. (2010) Mycoviruses: future therapeutic agents of invasive fungal infections in humans? Eur J Clin Microbiol Infect Dis 29: 755-763. https://doi.org/10.1007/s10096-010-0946-7

122. Tebbi CK (2014) Methods of inducing leukemia and lymphomas and detecting susceptibility to leukemia/lymphoma. United States patents US8623647B2.

123. Tebbi CK (2017) Screening methods for detection of susceptibility to leukemia and lymphomas. United States patents US9783785B2.