Carcinogenesis and Leukemogenesis of Microorganisms: A Review

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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>
<thead>
<tr>
<th>Virus</th>
<th>Viral Taxonomy</th>
<th>Genome</th>
<th>Possible association with cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV</td>
<td>Herpesviridae</td>
<td>dsDNA 172 kb–90 ORFs</td>
<td>BL, NPC, Lymphoma, HL</td>
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<td>Polyomaviridae</td>
<td>dsDNA ~5.2 kb</td>
<td>E, G, F, N, P, Li, O, Possible prostate</td>
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<td>HCC</td>
</tr>
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<td>Flaviviridae</td>
<td>dsRNA 9.4 kb 9 ORFs</td>
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<td>Retroviridae</td>
<td>dsRNA/DNA?</td>
<td>Seminomas, breast, GC, KS, Le, melanoma, P</td>
</tr>
<tr>
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<td>Retrovirdae</td>
<td>dsRNA</td>
<td>KS, NHL, HL, Cervical, Anal, Conjunctiva</td>
</tr>
<tr>
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<td>Retrovir</td>
<td>dsRNA/DNA?</td>
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</tr>
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<td>dsDNA 165 kb ~ 90 ORFs</td>
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<tr>
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<td>Circoviridae</td>
<td>ssDNA 3.8 kb</td>
<td>Cervical, lung, possible head and neck</td>
</tr>
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</table>

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 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 promoter 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 perturbation 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, Recoviridae, 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
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 transcriptome of virus-infected Malassezia restricta cells [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 "population-mixing" of both cancer and non-cancer genes. The "population-mixing" mechanism proposes that the establishment of a new host population involves the mixing of genetic material from different hosts, which can lead to the development of cancer. This mechanism is supported by studies that have shown a correlation between the occurrence of childhood cancers and the immigration of individuals from different countries. However, the exact details of how this mechanism contributes to the development of childhood cancers are not fully understood.

In addition to the "population-mixing" mechanism, other hypotheses for the role of infections in carcinogenesis have been proposed. These include the "infection-induced inflammation" theory, which suggests that infections can trigger inflammation, which in turn can promote the development of cancer, and the "infection-induced environmental changes" theory, which proposes that infections can alter the environmental conditions that promote cancer development.

In summary, the role of infections in carcinogenesis is complex and multifactorial, and further research is needed to fully understand the mechanisms by which infections contribute to the development of childhood cancers. However, it is clear that infections play a significant role in the development of these diseases, and understanding their role is crucial for developing effective prevention strategies.
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-retrovirinae 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 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.

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

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