African Journal of Basic & Applied Sciences 7 (4): 223-232, 2015
ISSN 2079-2034

DOI: 10.5829/idosi.ajbas.2015.7.4.1148

A Review on Gene Involved in Cancer Development and Oncogenic Viruses

Addisu Demeke Teklemariam, Girma Geleta and Asmelash Tassew

Addis Ababa University College of Veterianry Medicine and Agriculture, Debre Zeit, Ethiopia

Abstract: Oncogenic viruses are the viruses that cause cancers in their natural hosts or experimental animal systems which are thought to be causative agents of about 15-20% of cancers. They have been broadly classified into the DNA oncogenic viruses and RNA oncogenic viruses based on the nature of the nucleic acid contain within their virion. The oncogenic DNA and RNA viruses that have been identified both in animals and humans includes retroviruses, papillomaviruses, herpesviruses and other DNA viruses. Oncogenic viruses promote cellular transformation, prompt uncontrollable cell generation and lead to development of malignant tumors. Virtually all type of normal cells may undergo the changes that eventually create tumors. For better understanding of cancer, knowing the mechanisms through which cancers produced is important. Generally this paper gives highlight about some of the gens induced cancer and related oncogenic viruses.

Key words: Oncogenes · Oncogenesis · Virus

INTRODUCTION

Viruses are thought to be causative agent of about 15-20% of cancers, including some of the world's most common cancers [1]. Oncogenic viruses are significant pathogens for humans, farm animals and pets. These pathogens are classified into different virus families such as Herpesviridae, Adenoviridae, Poxviridae, Papillomaviridae, Hepadnaviridae, Polyomaviridae and Retroviridae [2]. Oncogenic viruses (tumor viruses) consist of both DNA and RNA viruses [3]. Unlike RNA tumor viruses, DNA tumor virus oncogenes encode viral proteins necessary for viral replication. RNA tumor viruses carry changed variants of normal host cell genes, which are not necessary for viral replication [4].

Oncogenic viruses promote cell transformation, prompt uncontrollable cell generation and lead to the development of malignant tumors. Virus promoted malignant transformations in cells are the first step in the complex oncogenic process equipped with strategies that promote the proliferation of infected host cells for their survival and replication [5].

In order to better understand cancer, it is helpful to know how tumors form. Usually cell growth and divide in a controlled and orderly manner. Under normal circumstance, the balance between cells reproduction and intimally programmed cell death (called apoptosis) is maintained by many natural mechanisms of the body [6]. The body tightly regulates both processes to ensure health organs and tissues. Sometimes, however, cells continue to reproduce even when new cells are not needed. Alterations and mutations in cell DNA can disrupt the orderly balance of cell reproduction and cell death, causing changes in the normal regulatory process. As a result of unregulated growth, a mass of tissue, called a tumor, can then develop [7].

Oncogenic viruses use various mechanisms to induce tumors, such as enhancing cellular oncogenes or inhibiting tumor suppressor genes. Oncogenesis is multi-stage process. Most cancers do not arise from mutation of a single gene but rather from cumulative accumulation of multiple genes mutations [8].

Mutations that contribute to tumor genesis generally occur in one of three types of genes; a proto-oncogene, a tumor suppressor genes, or genes involved in DNA replication and repair. The combination of oncogenes and tumor suppressor gene mutations occulting in multi stage process leads to transformation [9]. Therefore, the objective of this paper is to review oncogenic viruses and their mechanisms of action.

Corresponding Author: Addisu Demeke Teklemariam, Addis Ababa University College of Veterianry Medicine and Agriculture, Debre Zeit, Ethiopia. E-mail: ademeke16@yahoo.com.

Oncogenic Viruses of Animals

History of Oncogenic Viruses: In 1903, Borrel advanced the bold, even bizarre hypothesis for that time, of the infectious nature of certain cancers. Ellerman and Bang discovered avian leucosis virus (ALV) in 1908 and showed that the virus causes leukemia and lymphoma in chickens [10].

In 1909, a farmer brought Dr. Francis Peyton Rous, a junior faculty member then at Rockefeller University, a hen that had a breast tumor. Rous performed an autopsy, extracted tumor cells and injected the cells into other hens, which then developed sarcoma.

In Peyton Rous discovered sarcoma viruses. This was the first experimental proof of an infectious etiologic agent of cancer and the chicken sarcoma-inducing RNA virus was subsequently named the Rous sarcoma virus. After a half-century debate on whether viruses truly cause cancer, Rous was eventually awarded the Nobel Prize in Medicine and Physiology in 1966 for his discovery of tumor-inducing viruses [11].

In 1936, Bittner discovered that a' milk factors' is responsible for the mammary adeno carcinoma of the mouse. The Murine leukemia virus was discovered in 1951 by Gross and Harvey and Moloney isolated in 1964, the virus responsible for Murine sarcoma. In the same year, 1964, the feline leucosis virus was identified by Jarrett and in child lymphoma cell cultures, the Epstein Barr virus was identified [12]. In 1969, Theilen and Snyder discovered the feline sarcoma virus and Millner isolated the bovine leucosis virus. On year later Temin and Baltimore discovered the RNA dependent reverse transcriptase or DNA polymerase. In 1978, Fiers and Weissman published simultaneously the first genetic map of an oncogenic virus. On the same year Collect and Weissman identified the transformed proteins encode by the viral oncogene [13]. Subsequent studies in mammals and other hosts led to discoveries of other tumor-inducing viruses, some of which contained oncogenes in their genomes and others that did not [14].

Genes Involved in Cancer Development: Cancer is caused by the accumulation of genetic and epigenetic mutations in genes that normally play a role in the regulation of cell proliferation, thus leading to uncontrolled cell growth. Those cells with mutations that promote a growth and survival advantage over normal cells are selected, leading to the evolution of a tumor. Genes involved in tumorigenesis include those whose products: 1) directly regulate cell proliferation either promoting or inhibiting, 2) control programmed cell death or apoptosis and 3) are involved in the repair of damaged DNA. Depending on how they affect each processes, these genes can be grouped into three general categories: tumor suppressor genes (growth inhibitory), proto-oncogenes (growth promoting) and DNA repair genes [15].

Oncogenes: Cells contain many normal genes that are involved in regulating cell proliferation. Some of these genes can be mutated to forms that promote uncontrolled cell proliferation [16]. The normal forms of these genes are called proto-oncogenes, while the mutated, cancer causing forms are called oncogenes [5].

Oncogenes were originally found in retro viruses, where collectively referred to as v-Oncogenes (viral oncogenic genes). The term oncogenes is now applied broadly to any genetic element associated with cancer induction, including some cellular genes not known to have viral homologues and some DNA viruses genes not known to have cellular homologues [9].

Oncogenes actively promote proliferation (analogous to the gas pedal of the cell cycle). Mutations that convert proto-oncogenes to oncogenes typically increase the activity of the encoded protein or increase the expression of the normal gene. Such mutations are dominant or gain of function mutations. Therefore, only one copy of the gene needs to be mutated in order to promote cancer. Oncogenes were first identified in oncogenic retroviruses that had picked up a cellular oncogene (c-*onc*) and incorporated it into the viral genome to produce a viral oncogene (*v-onc*) [16].

Tumor Suppressor Genes: Tumor suppressor genes can be defined as genes which encode proteins that normally inhibit the formation of tumors. Their normal function is to inhibit cell proliferation, or act as the "brakes" for the cell cycle. Mutations in tumor suppressor genes contribute to the development of cancer by inactivating that inhibitory function. Mutations of this type are termed loss of function mutations. These genes prevent malignant transformation and called anti-oncogenes. When these genes lose their suppressive effects, unpreventable growth occurs [17].

Tumor suppressor genes may be divided into two general groups: promoters and caretakers. Promoters are the traditional tumor suppressors, like p53 and RB. Mutation of these genes leads to transformation by directly releasing the brakes on cellular proliferation. Caretaker genes are responsible for processes that ensure

the integrity of the genome, such as those involved in DNA repair. Although they do not directly control cell proliferation, cells with mutations in these genes are compromised in their ability to repair DNA damage and thus can acquire mutations in other genes, including proto-oncogenes, tumor suppressor genes and genes that control apoptosis. A disability in DNA repair can predispose cells to widespread mutations in the genome and thus to neoplastic transformation [16].

Mutator genes/DNA Repair Genes: Recently, a third class of cancer associated genes has been defined thanks to the analysis of tumors of particular type; that is, tumors in which an inherited mutated predisposing gene plays a significant role. These tumors include cancers in patients suffering from hereditary non polyposis colorectal cancer syndromes. The genes implicated in these tumors have been defined as mutator genes or genes involved in the DNA mis-match repair process. Although not directly recently, a third class of cancer associated genes has been defined thanks to the analysis of involved in the carcinogenesis process, these genes, when inactivated, expose the cells to a very high mutagenic load that eventually may involve the activation of oncogenes and the inactivation of tumor suppressors [2].

RNA Tumor Viruses: The oncogenic retroviruses (formerly called RNA tumor viruses) have played an important role in cancer research since their discovery in chickens 100 years ago. The discovery of retroviral oncogenes established the central paradigm that cancer is a genetic disease [18]. Retroviruses are large group of enveloped viruses associated with a variety of diseases in a wide range of host species. Avian retroviruses, the Rous sarcoma viruses (RSV) and ALV are historically known for their ability to induce a number of types of cancer in poultry [19].

Most retroviruses are RNA that can cause either leukemia or sarcoma (solid tumors that can metastasis in any organ of the body) and also known as leukoviruses or leukemia sarcoma viruses [20].

Most established oncogenic retroviruses, including, Human T-cell leukemia viruses, RSV, Abelson murine leukemia virus, Moloney murine leukemia virus, Murine mammary tumor virus, Bovine leucosis virus (BLV), Jaagsiekte sheep retrovirus (JSV) [21].

Several different mechanisms of oncogenesis have been associated with different classes of retroviruses. These classes of retroviruses are;

Acute Transforming Retroviruses: These are also called Transducing retroviruses or oncogene containing retroviruses. They are the oncogene containing retroviruses, such as the avian RSV, the Murine sarcoma viruses (MSV) and Abelson murine leukemia virus which all captured oncogenes from their hosts [18]. They encode oncogenes in their genome and thereby cause polyclonal tumors of virtually all infected cells [22].

Acutely transforming retroviruses are directly oncogenic by carrying an additional viral oncogene, v-onc and are classified as ‘’transuding retroviruses’’. The retroviral v-onc originate from a host c-onc gene and the transforming activity of the v-onc is accentuated by mutation. Given the high error rate of reverse transcription v-onc homologs of c-onc genes will always carry mutation and the strongly promoted production of the viral oncoprotein will readily exceed that of the normal cellular oncoprotein. The result can be uncontrolled cell growth [22].

Whenever acute transforming retroviruses integrate in the host genome, it is the v-onc that is directly responsible for the rapid malignant changes that occurs in cells infected with these viruses. Many acute retroviruses induce solid tumors in addition to hemopoietic tumors. These viruses are termed ‘sarcoma’ viruses. In addition to many avian leucosis virus derived sarcoma viruses that have incorporated various v-onc genes, several acute transforming defective sarcoma viruses have been isolated from sarcoma’s of cats naturally infected with exogenous feline leukemia virus, a woolly monkey infected with a simian retrovirus and several sarcoma viruses have been isolated from laboratory rodents with both exogenous and endogenous retroviruses [24].

Chronic Transforming Retroviruses: These are also called non acute transforming retroviruses, cis-activating retro viruses. Chronic transforming retroviruses are the second type of oncogenic retroviruses that does not contain genes derived from cellular sequence and typically induce tumors by integrating into the host genome and altering the expression of a cellular gene. The majority of these viruses induce tumors after a much longer latent period than viruses that contain v-onc genes with tumors arising several months or more after infection [20]. They cause dysregulated expression of cellular oncogenes up on integration of the provirus into the host genome and usually cause monoclonal tumors with latencies longer than those seen with acute retroviruses [22].

Chronic retroviruses are large number of viruses lacking oncogenes; including ALV, Murine leukemia viruses (MLV), feline leukemia virus and murine leukemia virus activate cellular oncogenes by insertional mutagenesis. They induce neoplasia through random integration into the host genome of somatic cells. They exert their effect as "cis-activating'' retroviruses that transform cells by becoming integrated into cell DNA close to a cell growth regulating gene and thus usurping normal cellular regulation of these [25].

The presence of an integrated provirus, with its strong promoter and enhancer elements, upstream from a c-onc may amplify the expression of the gene greatly. This is the likely mechanisms where by the weakly oncogenic endogenous avian leucosis viruses produce neoplasia, the viral genome generally become integrated at particular location, immediately upstream from a host c-oncogene. Integrated avian leucosis provirus increases the synthesis of normal c-myc oncogene product 30 to 100 fold [23].

Not all chronic transforming retroviruses require insertional mutagenesis retroviruses in regions of c-onc genes to be oncogenic. Both exogenous and endogenous mouse mammary tumor viruses carry an extra viral gene sequence that encodes a super-antigen (sag) that stimulates proliferation of lymphocyte. Expression of sag stimulates massive B cell proliferation and mouse mammary tumors virus replication is the dividing B cells with subsequent homing of virus-expressing lymphocyte to mammary tissue. Both lymphoma and mammary tumors may ensue, but oncogenesis does not require alteration of host oncogenes [26].

The exogenous ovine retrovirus that cause nasal sarcomas and pulmonary adenocarcinoma infect epithelial target cells and transformation is related to expression of the viral env-gene. This modified env-gene product stimulates cell growth [27].

Trans Activating Transforming Retroviruses: Trans activating transforming retroviruses encode proteins that contribute to transformation, but are not by themselves sufficient to induce full blown cellular transformation [26].

Bovine leukemia virus is an exogenous retrovirus that causes chronic leucosis and B-cell lymphoma. The virus encodes tax, rex.R3 and g4 genes in the 3' end of its viral genome. The tax gene functions as trans activator of host genes [23].

Mechanisms of Retroviruses to Induce Tumors: Oncogene capture: Oncogene capture is the process by which portions of c-onc genes are incorporated into retroviruses. The integration of the replication competent retroviruses into the host genome, an obligate step in the life cycle of all retroviruses, is the first step. Following integration, the viral genome is transcribed using cellular machinery and although most transcripts terminate in the 3'LTR, a fraction fail to do so and continue into flanking cellular sequence generating transcripts called read through transcripts. In case where the virus integration has occurred near a c-onc, the read through transcripts can contain these sequences and can lead to expression of the c-onc gene product [13].

The second step in oncogene capture involves the packaging of the read through transcript in virions that are released from the cell. Retrovirus virions contain two copies of the virus genome, a feature that necessary for successful replication following infection of cell. Reverse transcription requires both copies to generate the DNA copy that goes into integrates into the genomes. The final step in the process occurs after the virion containing one normal genome and one hybrid transcript infects new cell. As part of the reverse transcription process, the template switching between the two RNAs can lead to recombination and incorporation of the cellular sequence within the viral genome [25].

Insertional Mutagenesis: Many retroviruses do not contain oncogenes and viruses of this type are common in many species and exist naturally. They are the predominant cause of retroviral induced tumors outside of laboratory setting [13].

The oncogenic properties of these viruses reflect that fact integration is an obligatory part of the retro viral life cycle and these agents are insertional mutagens that disrupt the DNA structure at the site of integration. These disruptions can separate exons of the cellular genes, resulting in the production of non functional proteins or proteins with altered formation. They can also separate regulatory elements such as 3' untranslated sequences that control the stability of cellular the stability of cellular mRNAs from coding sequences. As consequences, altered expression of genes near integration sites can contribute to oncogenesis [28].

The second consequences of integration relates to the structure of the integrated provirus, which has strong promoter and enhancer sequences with in the long terminal repeats that are located at both ends of the genome. The LTRs also contain other regulatory sequences such as polyadenylation sequences that are required for proper expression of viral RNAs.

These sequences allow the virus to integrate more or less randomly in the host genome and express the viral genes [24].

Activation of Cellular Micro RNAs (Promoter Insertion): The third type of oncogenesis involves activation of cellular mRNAs, either by insertional mutagenesis (ALV and MLV) or by transcription activation (endotheliosis virus) [29]. The first clues to the mechanisms were presence of common integration sites in all cells, demonstrating aclonal relationship and indicating that the cells in the tumors arose from a single virus infected cell. Further studies showed that the tumors contained novel fusions mRNAs with both viral and cellular sequences [30].

In most tumors, the provirus had integrated into the first intron c-myc, downstream of a transcriptional pause site. Surprising, the 3' LTR drove transcription of the downstream cellular myc gene by mechanism called "promoter insertion'' [31]. The 5' was not used in these tumors because of mutations downstream of the 5'LRT which is somehow in activated it, Since the first c-myc exon is non coding. This resulted in over expression of the normal cellular mycoprotein, a transcription factor that is normally expressed only briefly during the cell cycle [32].

Envelop Signaling: The fourth type of viral oncogenesis involves signaling by the viral *env*-glycoprotein genes and is used by friend spleen focus forming virus and Jaagsiekte sheep virus (JSV) [33].

Accessory Genes: The accessory or non structural genes of the human t-lymphotropic virus and bovine leukemia virus such as tax and HBZ are key to cancer induction by these agents [19].

DNA Tumor Viruses: Although retroviruses are the most important oncogenic viruses in animals, certain DNA viruses are also important as known cause of cancers [34]. The successful replication of mammalian DNA viruses such as polyomaviruses, adenoviruses and herpesviruses require viral adaptation of the host cell to establish an environment that can accommodate the increased demands for nutrients, energy and macro molecular synthesis that accompany viral infection [35].

Herpesvirus: Over 200 Herpesviruses that are known to infect humans and a spectrum of animal species including oysters are classified under Herpesviridae due to common characteristics such as double stranded, linear DNA genomes encoding 100-200 genes encased within an icosahedral capsid, which is itself wrapped in the tegument protein layer containing both viral proteins and viral mRNA's and a lipid bilayer envelope bearing many viral glycoproteins [36].

Marek's disease virus (MDV) is a lymphotropic alpha herpesvirus that induces fatal rapid onset T-cell in lymphoma genesis and acts as a regular of transcription [37]. Marek's disease virus or gallid herpesvirus 2 is highly contagious herpes virus whose infection affects predominantly chickens as well as other avian species such as turkeys, pheasants, quail and game fowl worldwide. It is characterized by the T-cell lymphoma infiltrating the nerves, organ, muscle and epithelial cells leading to paralysis of legs, wings and neck, loss of weight and vision impairment [16].

MDV replicates in B and T lymphocytes during early cytolytic infection and subsequently establishes a latent infection of T lymphocytes that are finally transformed, which leads to the development of lymphomatous lesions in the visceral organs, peripheral nerves and skin. Marek's Diseases, therefore, serves as an elegant model for understanding the molecular mechanisms of herpesvirus induced latency and oncogenesis [38].

MDV genome encodes at least 80 proteins, among which Meq is considered to be the major oncoptotein. Meq is a protein of 339 amino acids that is expressed during both the cytolytic and latent or tumor phase of infection. Over expression of Meq results in the transformation of fibroblast cells. The Meq oncoprotein interacts directly with P53 and inhibits P53 mediated transcription activity and apoptosis [39]. Although MDV is alpha herpesvirus, biologically it more closely resembles the lymphotropic oncogenic gamma herpesviruses, such as Epstein Barr virus, Kaposi's sarcoma associated herpesvirus and herpesvirus saimiri [40].

The Gamma herpesvirinae are a subfamily of lymphotropic herpesviruses that infect and replicate mainly in lymphoid cells and are capable of causing cellular transformation. Importantly viruses belonging to this subfamily have been associated with in both human and non human primates [41].

Papillomavirus: Papillomaviruses are DNA viruses that can integrate into cells, activate the expression of normal cellular genes and ultimately cause over expression or inactivation of genes that can lead to cellular transformation or uncontrolled growth. Papillomaviruses

are oncogenic, contagious and infectious and have been described in a number of species. These viruses are considered species specific, human, bovine, canine and feline isolates lack serological cross reactivity [42].

Papillomaviruses produce papilloma (warts) on the skin and mucous membranes of most animal species. These benign tumors are hyperplastic out growth that generally regresses spontaneously. Occasionally, however, they may progress to malignancy. Papilloma or warts are seen more commonly in cattle than in any other domestic animal. All ages are affected, but the incidence is highest in calves' and yearlings [43]. BPV 1 and 2 exhibit a some what broader host range and tissue tropism than other types causing fibropapilloma and sarcoids in horses. Transmission from cattle to humans was suspected from the incidence of cutaneous warts in butchers; however, the virus isolated from these people does not appear to be related to any known bovinevirus [34].

Different papillomaviruses are associated with the development of tumors in different sites. Bovine Papillomavirus (BPV) type 1 and less commonly BPV 2 are widely recognized as causative agents of equine sarcoids. This is based on facts that BPV 1or 2 DNA is detected in the majority of sarcoids tumors, BPV genes are expressed in sarcoids, experimental inoculation of equine sarcoids with BPV induce sarcoids like lesions in horse and BPV DNA can transform primary equine fibroblasts *in vitro*. However, it remains unclear to what extent BPV 1 proteins are involved in the transformation of equine cells [44].

Humans can be infected with Human papillomaviruses. Persistent infection with high risk of these viruses are recognized as the major cause of cervical cancer, which is the second most common among women worldwide and the leading cause of death from cancer among women in developing countries [45].

In papillomavirus induced cancers the viral DNA is integrated into that of the host. This integration probably is necessary for malignant transformation, as the pattern of integration is clonal with cancers. The E6 and E7 are expressed up on initial papillomaviruses infection of the host keratinocytes. These proteins are largely responsible for modulating cell cycle progression and act as oncoproteins [46].

One of the well characterized interactions in the binding of E6 proteins to the tumor suppressor protein P53, affecting P53 dependent cell cycle regulation. The P53 protein is important in regulating the G1/S and G2/M cell cycle check points following DNA damages [47]. For some papillomaviruses, integration disrupts one of the early genes, E2, which is a viral repressor. But the viral oncogenes (examples, E6 and E7) remain intact, are expressed efficiently and cause the malignant transformation. The proteins expressed by the viral oncogenes interact with cellular growth regulating proteins produced by proto-oncogenes and tumor suppressor P53 to block apoptosis and promote cellular proliferation. In case of BPV 1 E5 oncoprotein, alters the activity of cell membrane proteins involved in regulating cellular proliferation [46].

Polyomavirus: Polyoma viruses are small, icosahedral non enveloped DNA viruses that infect a large number of vertebrates. Founding member of the polyomaviruses, murine polyomaviruses was identified by Luck Gross in 1953 when, searching for cell free transmission of leukemia, he found a filterable agent capable of inducing salivary gland tumors in new born mice. This new virus became the archetypal member of the polyomaviridae family [48].

The first polyomavirus that has been identified in mice in early 1950's is the K virus (now known as the Murine pneumotropic virus) and the murine polyomavirus. The name polyomavirus, however, was first given in 1958 due to its ability to produce a variety of solid tumors. Depending on the type of host cell infection, polyomaviruses can either induce cellular transformation or tumorigenesis or produce infectious virion with subsequent cell lyses. These viruses encode proteins that oncogenically transform cells in culture, induce tumors formation in infected and transgenic mice and have been reported to be associated with human cancers [49].

Polyomaviruses have been identified in many hosts including humans, birds, monkeys and hamsters; each virus exhibits a relatively narrow host range. Some strains of murine polyomavirus are highly tumorigenic in mice while infection with others results in a lower incidence of tumors formation [50].

Polyomaviruses are dependent on the DNA replication machinery of the host cell for viral replication. Since the viruses infect quiescent (non dividing) cells, the outcome of an infection is dependent on the ability of the virus to induce the host cell to inter S-phase in the absence of mitogenic signals [51].

The interaction between the T antigen (TAg) and the PBR family proteins results in the activation of E2F family of transcription factors, which induce expression of cellular genes essential for entry to S-phase and DNA synthesis. TAg also inactivates the P53 tumor suppressor to promote the transition of cells from G1 to S and to

prevent apoptosis. In permissive host this leads to progeny virion production followed by cell lyses and death. In a non permissive host or if rearrangements in the viral chromosome occur interfere with replication, it can result in oncogenesis, since T antigens are being continuously expressed but the viral life cycle cannot go to completion. The third potential mechanism of Tag mediated oncogenesis is the induction of chromosomes damage, but the exact mechanism of how polyoma viruses initiate this event is still not understood [48]. The middle T antigen (mTAg) which is phosphoprotein is also responsible for many of transformation function of polyoma virus. It is potent oncoprotein that has the ability to transform several established cell types in culture and can induce variety of tumors in animals in dependent of TAg. However, for the transformation of primary fibroblasts, mTAg is dependent on Tag [52].

Adenovirus: Adenovirus family is large and contains member that infect a wide range of animals, including monkeys, livestock, mice, bird and humans. The family Adenoviridae comprise two genera; the genus Mast adenovirus comprising viruses that infect mammalian species and the Avian adenovirus comprising viruses that infect bird [39].

Adenoviruses are being used as gene delivery vehicles for cancer therapy, gene therapy and genetic immunization studies. They are attractive because recombinant, replication defective viruses possess the advantages of high transduction efficiencies of many cell types and high levels of short-term expression of transduced genes [53].

According to classical concepts of viral oncogenesis, the persistence of virus specific oncogenes is required to maintain the transformed cellular phenotype. In contrast in the case of adenoviruses, the viruses can mediate cellular transformation through the initial 'hit' while maintenance of transformed state is compatible with the loss (run) of viral molecules. That is adenovirus may contribute to the development of some tumors through mutagenesis or alteration based on "hit and run mechanism'' resulting in tumors that do not carry viral genes and proteins [54].

The first early region expressed after adenovirus infection is the immediately early transcription unit E1A since it requires only cellular proteins for its expression. Their E1A gene products in turn activate transcription from the other early promoter genes. The E1A genes is comprised of two exons and several E1A polypeptides are produced following alternative splicing of a primary RNA transcript [55].

The E1A gene products exert their effects by interactions with numerous cellular proteins, many of which are involved in transcriptional regulation**.** The E1A products interact with important cellular proteins retinoblastoma tumor suppressor, PRB and related family members of P107 and P30 via CR1 and CR2. The expression of E1A alone is sufficient to induce immortalization of primary rodent cells. E1A fully transform such cells in conjunction with other oncogenes such as E1B proteins or activated ras [56].

Poxviruses: Poxviruses are large DNA viruses that replicate exclusively in the cytoplasm. Among the poxvirus family, only three viruses are known to be responsible for tumorigenesis; Shope poxvirus, Molluscum contagiosum virus and Yaba monkey tumor virus [8].

Molluscum contagiosum is specifically a human disease, but it is often confused with zoonotic poxviruses. Infection is characterized by multiple discrete nodules two to five millimeters in diameter, limited to epidermis and occurring anywhere on the body except on the soles and palms [34].

The Yaba poxvirus was discovered because it produced large benign tumors on the hairless areas of the face, on the palms and inters digital areas and on the mucosal surfaces of the nostrils, sinuses, lips and palate of Asian monkeys (*Cercopithecus aethiops*) kept in a laboratory in Nigeria. The virus is zoonotic, spreading to humans in contact with diseased monkeys and causing similar lesions as in affected monkeys [57].

How poxviruses induce tumors remain unknown, as no similarity has been found between poxvirus genomes and oncogenes exist in other viral families. However, many poxviruses encode a homologue of the epidermal growth factor and transforming growth factor alpha. This homologue is best characterized by vacciniavirus, myxomavirus and Shope Fibromavirus, where it is referred to as vaccinia growth factor, myxoma growth factor and shope fibroma growth factor respectively [58].

Hepadnaviruses: Hepadnaviruses are a family of small, enveloped DNA viruses that productively infect hepatocytes, the major cell type of the liver. The prototype virus of this family is hepatitis B virus, which infects humans and higher primates. Closely related viruses are found in the wooly monkey, wood chuck and beechey ground squirrel [58]. Mammalian, but not avian, hepadna viruses are associated strongly with naturally occurring hepato-cellular carcinomas in their natural

hosts. Chronically infected woodchucks almost inevitably develop carcinoma even in the absence of other carcinogenic factors. Duck hepatitis virus is probably not oncogenic by itself, but its integrated DNA has been found in mycotoxin associated hepato cellular carcinomas in peking ducks [23].

Oncogenesis by mammalian hepadnaviruses is multi factorial process. These viruses contain a protein, HBx, which stimulates transcription of many growth activating host cells genes (examples, c-myc and c-fos) and possibly inhibits cellular growth suppressor proteins [60].

CONCLUSIONS AND RECOMMENDATIONS

Generally, the mechanisms by which RNA and DNA viruses induce cancer in animals are different but there are also several common themes shared by these viruses. The revolution in the molecular cell biology during the last few years have provided remarkable insights into the mechanisms of regulation of cell growth and differentiation and this insights have, in turn, our understanding of the mechanism under pinning failures of regulatory processes that expressed as cancer. Both DNA and RNA oncogenic viruses are the cause of important oncogenic diseases in animals, poultry and humans.

ACKNOWLEDGEMENTS

I would like to express my sincere appreciation to all of the journals which are of used as a good source of information to write this review.

REFERENCES

1. Yokota, J., 2000. Tumor progression and metastasis. Carcinogen., 21: 497-503.
2. Truyen, U. and M. Lochelt, 2006. Relevant oncogenic viruses in veterinary medicine: original pathogens and animal models for human disease. Contrib. Microbiol., 13: 101-117.
3. Klein, G., 2002. Perspectives in studies of human tumor viruses. Fro. Biol. Sci., 7: 268-274.
4. Judson, H., B. Lewin, G. Stent and J. Watson, 1994. Basic genetic Mechanisms. In: Albert's, B., Bray, D., Lewis, J., Raff, M., Roberts, K., Watson, J. (ed.): Molecular Biology of the Cell. 3rd ed., Garland Science, New York, USA, pp: 273-287.
5. Sevik, M., 2012. Oncogenic viruses and mechanisms of oncogenesis. Vet. Anim. Sci., 36(4): 323-329.
6. Iacovides, D., S. Michael, C. Achilleos and K. Strati, 2013. Shared mechanisms in stemness and carcinogenesis: lessons from oncogenic viruses.. J. Virol., 68(2): 3389.
7. Crump, K. and D. Thamm, 2011. Cancer Chemotherapy for the Veterinary Health Team. Blackwell. Iowa, USA.
8. Sabourdy, F., A. Casteignau, J. Gelfi, S. Deceroi, M. Delverdier and F. Messud-Petit, 2004. Tumorigenic poxviruses: growth factors in a viral context. J. Virol., 85: 3597-3606.
9. Chow, A., 2010. Cell Cycle Control by Oncogenes and Tumor suppressors: Driving the transformation of normal cells into Cancerous cells. Nat. Edu., 3(9): 7.
10. Braoudaki, M. and F. Tzortzatou-Stathopoulou, 2011. Tumorigenesis related to retroviral infections. J. Infect. Dev. Ctries., 5(11): 751-758.
11. Javier, R. and J. Butel, 2008. The history of tumor virology.Canc. Res., 68: 7693-7706.
12. Javier, R. and J. Butel, 2009. The history of tumor virology.Canc. Res., 68: 7693-7706.
13. Rosenberg, N. and P. Jolicoeur, 1997. Retrovirus pathogenesis. In: Coffin, J., Hughes, S., Varmus, H. (ed.): Retroviruses. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, USA, pp: 475-586.
14. Kalland, K., Ke, X. and A. Øyan, 2009. Tumour virology history, status and future challenges. APMIS, 117: 382-399.
15. Hanahan, D. and R. Weinberg, 2000. The Hallmarks of Cancer. Cell, 100: 57-70.
16. Kumar, V., A. Abbas and N. Fausto, 2005. Oncogenes and Tumor Suppressor Genes. In: Cotran Pathologic Basis of Disease.7th ed., Elsevier/Saunders, New York, USA, pp: 292-306.
17. Fearon, E., 1998. Tumor suppressor genes. In: Vogelstein, B. and Kinzler, K. (ed.): The genetic basis of human cancer. McGraw-Hill Companies, USA, pp: 229-236.
18. Beemon, K. and N. Rosenberg, 2012. Mechanisms of Oncogenesis by Avian and Murine Retroviruses. In: Robertson, E. (ed.) : cancer associated viruses. Spring publishing. New York, USA, pp: 739-754.
19. Yao, W., L. Smith and V. Nair, 2014. An Avian Retrovirus Uses Canonical Generate Viral Micro RNA Expression and Processing Mechanisms To Generate Viral Micro RNA. J. Virol., 88(1): 2.
20. Stocking, C. and C. Kozak, 2008. Murine endogenous retroviruses. Cell Mol. Life Sci., 65(21): 3383-3398.
21. Braoudaki, M. and F. Tzortzatou-Stathopoulou, 2012. Tumorigenesis related to retroviral infections. J. Infect. Dev. Ctries., 5(11):751-758.

22. Ross, S., 2010. Mouse mammary tumor virus molecular biology and oncogenesis. Vir., 2: 2000-2012.
23. Maclachlan, N. and E. Dubovi, 2011. Fenner's Veterinary Virology. 4th ed. Saunders. London, UK, pp: 123-132.
24. Maeda, N., H. Fan and Y. Yoshikai, 2008. Oncogenesis by retroviruses: old and new paradigms. Rev. Med. Virol., 18: 387-405.
25. Bushman, F., M. Lewinski, A. Ciuffi, S. Barr, J. Leipzig, S. Hannenhalli and C. Hoffmann, 2005. Genome wide analysis of retroviral DNA integration. Nat. Rev. Microbiol., 3(11): 848-858.
26. Coffin, J., 2004. Evolution of retroviruses: Fossils in our DNA. Proc. Am. Philos. Soc., 148(3): 264-280.
27. Johnson, C. and K. Sanders, 2010. Jaagsiekte sheep retrovirus transformation in Madin-Darby canine kidney epithelial cell three-dimensional culture. J. Virol., 84(10): 5379-5390.
28. Morrison, H., B. Soni and J. Lenz, 1995. Long terminal repeat enhancer core sequences in proviruses adjacent to T-cell lymphomas induced by a murine retrovirus. J. Virol., 69(1): 446-455.
29. Lander, J. and H. Fan, 1997. Low frequency loss of heterozygosity in Moloney murine leukemia Virus induced tumors in BRAKF1/J mice. J. Virol., 71: 3940-3952.
30. Neil, J. and M. Stewart, 2011. Retroviruses as tools to identify oncogenes and tumor suppressor genes. In: Dudley, J. (ed.): Retroviruses and insights into cancer. Springer, New York, USA, pp: 285-306.
31. Hayward, W., B. Neel and S. Astrin, 1981. Activation of a cellular oncogene by promoter insertion in ALV-induced lymphoid leucosis. Nat., 290: 475-480.
32. Tam, W., S. Hughes, W. Hayward and P. Besmer, 2002. Avian bic, a gene isolated from a common retroviral site in avian leukosis virus-induced lymphomas that encodes a non coding RNA, cooperates with c-myc in lymphomagenesis and erythroleukemogenesis. J. Virol., 76(9): 4275-4286.
33. Leroux, C., N. Girard, V. Cottin, T. Greenland, J. Mornex and F. Archer, 2007. Jaagsiekte sheep retrovirus (JSRV): from virus to lung cancer in sheep. Vet. Res., 38: 211-228.
34. Murphy, F., E. Gibbs, M. Horzinek and M. Studdert, 1999. Veterinary Virology. 3rd ed., Academic Press. New York, USA, pp: 11-37.
35. Shea, C., 2005. DNA tumor viruses: The spies who lyse us. Curr. Opin. Genet. Dev., 15: 18-26.
36. Akula, S., F. Wang, J. Vieira and B. Chandran, 2001. Human herpes virus 8 interaction with target cells involves heparan sulfate. Virol., 282: 245-255.
37. Chbab, N., A. Egerer, I. Veiga, K. Jarosinski and N. Osterrieder, 2010. Viral control of VTR expression is critical for efficient Formation and dissemination of lymphoma induced by Marek's disease virus (MDV). Vet. Res., 41: 56.
38. Osterrieder, N., J. Kamil, R. Schumache, B. Tischer and S. Trapp, 2006. Marek's disease virus: from miasma to model. Nat. Rev. Microbiol., 4: 283-294.
39. Deng, X., X. Li, Y. Shen, Y. Qiu, Z. Shi, D. Shao, Y. Jin, H. Chen, C. Ding, L. Li, P. Chen and Z. Ma, 2010. The Meqoncoprotein of Marek's disease virus interacts with p53 and inhibits its transcriptional and apoptotic activities. J. Virol., 7: 348.
40. Liu, J. and H. Kung, 2000. Marek's disease herpesvirus transforming protein MEQ: a c-Jun analogue with an alternative life style. Vir. Gen., 21: 51-64.
41. Estep, R. and S. Wong, 2012. Non Human primate gamma-herpes viruses and their role in cancer. In: Robertson, E. (ed.): Cancer Associated Viruses. Springer Publishing, New York, USA, pp: 201-214.
42. Henry, C. and M. Higginbotham, 2010. Cancer Management in Small Animal Practice. Elsevier press. Maryland Heights, USA.
43. Howley, P. and D. Lowy, 2001. Papilloma viruses and their replication. In: Knipe, D. and Howley, P. (ed.): Fields virology. Vol. 2, 4th ed. Lippincott, Williams & Wilkins, Philadelphia, USA, pp: 2197.
44. Yuan, Z., E. Gault, S. Campo and L. Nasir, 2011. Different contribution of bovine papilloma virus type 1 oncoproteins to the transformation of equine fibroblast. J. Virol. , 92: 773-783.
45. Hausen, H., 2002. Papillomaviruses and cancer: from basic studies to clinical application. Nat. Rev. Canc., 2: 342-350.
46. Marchetti, B., E. Gault, M. Cortese, Z. Yuan, S. Ellis, L. Nasir and M. Campo, 2009. Bovine papillomavirus type I oncoprotein E5 inhibits equine MHC class I and interacts with equine MHC I heavy chain. J. Gen. Virol., 90: 2865-2870.
47. Finlay, M., Z. Yuan, I. Morgan, M. Campo and L. Nasir, 2012. Equine sarcoids: Bovine Papillomavirus type 1 transformed fibroblasts are sensitive to cisplatin and UVB induced apoptosis and show aberrant expression of pp: 53. Vet. Res., 43: 81.

48. Gjoerup, O., 2012. Polyomaviruses and cancer. In: Robertson, E. (ed.): Cancer associated viruses. Springer Publishing, New York, USA, pp: 337-376.
49. Dahl, J., J. You and T. Benjamin, 2005. Induction and utilization of an ATM signaling pathway by polyomavirus. J. Virol., 79(20): 13007-13017.
50. Kean, J. and R. Garcea, 2009. Polyomaviruses and disease. In: Damania, B. and Pipas, J. (ed.): DNA Tumor viruses. Springer Publishing, New York, USA, pp: 53-74.
51. Brown, A., L. Smith, L. Kgosana, J. Susan, B. Nair and M. All-day, 2009. Homodimerization of the Meq Viral Oncoprotein is necessary for induction of T-Cell Lymphoma by Marek's Disease Virus. J. Virol., 83(21): 11142.
52. Fluck, M. and B. Schaffhausen, 2009. Lessons in signaling and tumorigenesis from polyomavirus middle T antigen. Microbiol. Mol. Biol. Rev., 73(3): 542-563.
53. Brooks, G., K. Carrol, J. Butel, and S. Morse, 2007. Medical Microbiology. 24th ed., Jawetz, Melnick and Adelberg's. McGraw-Hill, New York, USA, pp: 55-63.
54. Nevels, M., B. Täuber, T. Spruss, H. Wolf and T. Dobner, 2001. ''Hit and run'' transformation by Adeno virus oncogenes. J. Virol., 75(7): 3089-3094.
55. Berk, A., 2005. Recent lessons in gene expression, cell cycle control and cell biology fromadeno virus. Oncogen., 24: 7673-7685.
56. Hearing, P., 2009. Adenovirus Transformation. In: Damania, B. and Pipas, J. (ed.): DNA tumor viruses. Springer Publishing, New York, USA, pp: 145-162.
57. Barrett, J. and G. Fadden, 2008. Yata pox viruses. In: Mahy, B. and Regenmortal, M. (ed.): Desk Encyclopedia of Animal and Bacterial Virology. San Diego, USA, pp: 392-393.
58. Chang, W., C. Upton, S.L. Hu, A. Purchio and G. McFadden, 1987. The genome of Shope fibroma virus, a tumorigenic poxvirus, contains a growth factor gene with sequence similarity to those encoding epidermal growth factor and transforming growth factor alpha. Mol. Cell Biol., 7: 535-540.
59. Prassolov, A., H. Hohenberg, T. Kalinina, C. Schneider, L. Cova O. Krone, K. Frolich, H. Will and H. Sirma, 2003. New hepatitis B virus of cranes that has an unexpected broad host range. J. Virol., 77: 1964-1976.
60. Mason, W., H. Low, C. Xu, C. Aldrich, C. Scougall, A. Grosse, A. Clouston, D. Chavez, S. Litwin, S. Peri, A. Jilbert and R. Lanford, 2009. Detection of clonally expanded hepatocytes in chimpanzees with chronic hepatitis B virus infection. J. Virol., 83: 8396-8408.