World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 4.223

HUMAN RETROVIRUSES AND MODERN CANCER RESEARCH: A REVIEW

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Article Received on 07/06/2017 **Article Revised on 28/06/2017** **Article Accepted on 19/07/2017**

ABSTRACT

The retroviridae family (retroviruses) consists of viruses which require an additional step of reverse transcription during their replication cycle. Cancer and related diseases make up one of the most prevalent causes of mortality. Around 20% of total cancer burden is due to chronic infections and around 15% of cancers are related to viral agents with a higher incidence rate in developing countries. Several human cancers and related malignancies are associated with retroviruses including HIV, breast cancer, prostate cancer and others. Chromosomes in human genome have a number of endogenous retroviral genomes that comprise the human genome. The phylogenetic linkage analysis shows a wide range of oncogenic elements linked to human indigenous retroviruses. They comprise around 1-8% of human genome and follow Mendelian patterns of inheritance. Retroviruses are being employed in newly emerging techniques like gene therapy as delivery vectors. The advanced molecular biology tools and sequencing techniques to analyze retroviruses have opened new horizons in tackling the global cancer burden.

KEYWORDS: Retroviruses, cancer, human endogenous retroviruses, human exogenous retroviruses, anti-retroviral therapy and gene therapy.

INTRODUCTION

Retroviruses or the retroviridae family consists of a number of viruses which require an additional step of reverse transcription during their replication cycle (Gordon, 2005). "Retro" is a Latin word for "backwards" and is used to refer to the process of reverse transcription during which these viruses create a DNA copy of their RNA genome. Basically, the Retroviruses are single stranded RNA viruses and have an intermediate form of DNA for replication. The host cells cannot utilize RNA genome for protein synthesis, thus the viral replication system need to synthesize the DNA copy of genome. The discovery of Retroviridae took place when their presence was identified in the tumor growths of several animal species and it became apparent that they were also abundant in human genomes. They comprise around 1-8% of human genome and follow Mendelian patterns of inheritance while passing from one generation to another (McLaughlin, 2008). There are total of seven genera of retroviridae that have been detected so far and among them the lentiviruses are of great importance as they are responsible for most of the retroviral diseases in humans, including human immunodeficiency virus (HIV- type one and two). The other important genus is oncoviruses that include human T- lymphotropic virus (Gordon, 2005).

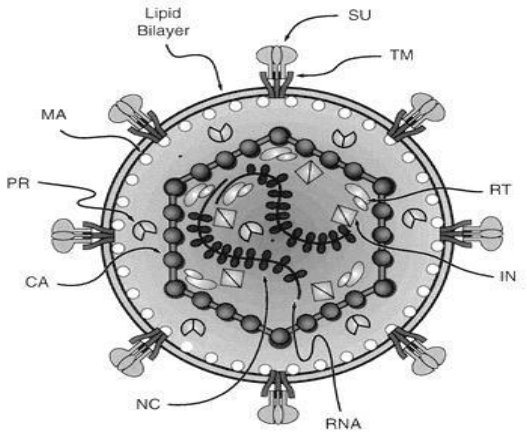

Fig. 1: Cross-Section of a Retrovirus Particle and associated proteins: NC, CA, IN, RT, MA, PR, SU and TM.

The cross-sectional analysis of the retroviruses show that they are enveloped particles (Figure 1). The envelope is made up of lipid bilayer which is cellularly derived from the host membrane and this is where the viral genome interacts with the host cells. The env region has transmemberane TM and surface SU proteins that are bound together through disulfide bonding. Proteins NC, CA, and MA are also products of enzyme action (Coffin,

1997). The incorporation of the retroviral genome occurs during the infection of the host cells. When this incorporation occurs in the germ line cells, they are called endogenous retroviruses as they constitute a portion of the genome after their incorporation. There are several viral sequences in the human genome that belong to old retroviruses. The exact origin of these viruses is not clear yet but it is thought that these viral sequences are the remains of very ancient infectious diseases. Deep analysis has shown that they are similar to the exogenous retrovirus sequences that cause diseases in animal as well as humans (Gordon, 2005). Now with the new advancements, the footprint of the ancient indigenous retroviruses can be traced through modern molecular biology techniques to a common ancestor (Rasmussen, 1996).

Cancer was recognized as an ailment thousands of years ago, and since then theories regarding cancer origin started to spread but nothing concrete was found up until the twentieth century. It is believed that the oldest evidence of cancer in humans came from the bones of four-million-year-old fossil remains (Diamandopoulos, 1996). Various kinds of cancers were found in the ancient Egyptian mummies that were as old as 3000 BC. Cancer was historically documented in the Code of Hammurabi in Babylon around 1700 BC and a number of other ancient manuscripts found over the time. Mostly the treatment involved invoking ancient priests and various herbs. The cause was dismissed by stating that it was the will of God and no further investigation was required. Everything changed with the dawn of scientific era and various factors, including viruses were investigated as the causative agents behind cancer (Mackay, 2006). During the 16th century, two doctors from Holland, Lusitani and Tulp, claimed that cancer was actually contagious. They came to this finding with the observation that a number of women could acquire breast cancer in one family. They contributed in the development of the contagion theory and suggested that cancer patients should be treated in isolation. This concept prevailed for a long time and the first cancer hospital in France in 1779 was forced out of the city out of fear of spreading cancer to the general population of France (Gardner, 2008). It is reported that around half a million cancer cases emerge in the USA annually. World Health Organization (WHO) reports that around 20% of total cancer burden is due to chronic infections and around 15% of cancers are related to viral agents and it has a higher incidence rate in third world countries (WHO report, 2014). The discovery of viruses as the causative agents of human cancers was one of the crucial discoveries of recent times. This discovery has opened new ways to approach cancer from prevention to treatment and has given a new understanding. With new advancements, the field of oncology continues to hunt for new causative agents as well as new therapeutic ways to combat cancer (Bergonzini, 2010).

The historic "war on cancer" in 1970 marks the discovery of retroviral reverse transcriptase which began the race to identify cancer causing human retroviruses. After the discovery of HTLV-1 in 1978, many detailed reports were published that provided additional information. The evidence of DNA provirus integration emerged with the serological assays that were performed on specific HTLV-1 antibodies (Gallo, 2005). Gallo laboratory has been credited for not giving up on the search even after many controversial claims emerged during the crusade and kept developing innovative specified assays and cell culturing techniques. They end up publishing the report in 1980 with identification and characterization of HTLV through a lymphoma T-cell line. After the identification of the adult T-cell leukemia (ATL), later researches concluded that HTLV was the causative agent. HTLV type 1 is thought to infect 4-10 million people around the world and 5% of such cases will also develop ATL (Weiss, 2001). Despite the advancements in the fields of virology and oncology, there has been no reduction in the mortality rates around the world in ATL cases. However, the techniques developed to aid the discovery of these pathogens paved the way to the identification of the etiology of AIDS (Coffin, 2015).

Retroviruses or the oncogenic viruses are significant in the field of oncology for two reasons. Firstly, it is reported that around 20% of cancer incidents in humans worldwide is thought to be related to viral infections (Goedert, 2000). If these infections are controlled significantly, the cancer burden worldwide can be reduced. Secondly, there are a number of cancer studies being conducted all around the world in which these viruses are being used to gain a better understanding of the mechanisms behind human cancers. The breakthrough studies of retroviruses in the context of oncology have been acknowledged with three Nobel Prizes which include the crucial discovery of reverse transcriptase, eponymous sarcoma virus and retroviral oncogenes (Wiess, 2001).

Organization and Genomic Structure

The retroviral genomic structure is very complex in nature. It is mostly linear and non-segmented. It consists of 7 to 15 kb of single stranded RNA which encodes three genes; gag, pol and then env (O'Keefe, 2013). A poly-protein is encoded by the gag gene which is translated from mRNA and cleaved with the aid of viral protease enzyme. The cleavage products include NC, CA, and MA proteins (Freed, 2001). Another poly-protein is encoded by the env gene which is cleaved into surface envelope glycoprotein gp120 and transmembrane glycoprotein gp41. Gag-pol glygoprotien is encoded by the pol gene and it encodes three enzymes; IN, RT and PR which are bounded to viral genome in the virion. The more complex retroviruses also encode accessory proteins like Nef, Vpu, Vif and Vpr. When the provirus is integrated, it has 5' end and 3' end long terminal repeats with U3, U5 and R distinct regions. An important

sequence called psi (ψ) acts as the packaging signal (Fanales-Belasio, 2010).

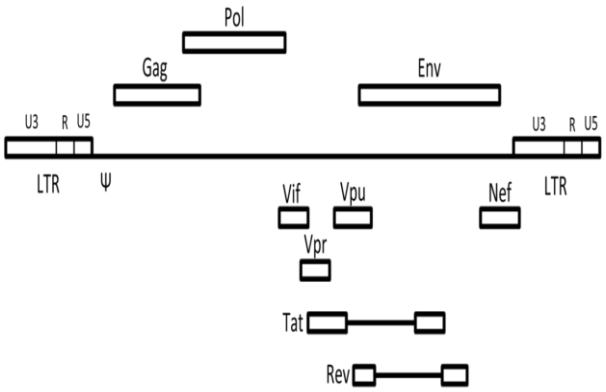

Fig. 2: Retrovirus Genome Structure.

Retroviral Replication

The retroviral attachment with the host cell begins with the help of knoblike viral protein structures (Env) that interact with the specific cell receptors on the host cell surface (O'Keefe, 2013). After that the fusion between the virus particle and host membrane occurs followed by genomic penetration. Reverse transcriptase is required in the production of a DNA copy of the genome which is then transported to the nucleus of the host cell as the site of viral integration. This is carried out with the help of IN protein (Freed, 2001). At this point, the viral DNA genome is called the Provirus and can be transcribed into RNA which is needed to create more viral RNA or viral proteins. Translation is accompanied by processing and subsequent assembly of virions. Structural proteins are used in packaging of viral particles and then maturation occurs. This happens when the polyprotiens, Gag and Gag pol are broken down by protease enzyme of the virus. The packaging is done from the host membrane which is cellular derived. The host cell starts to bud and finally the mature progeny is released from the host cell (Gordon, 2005).

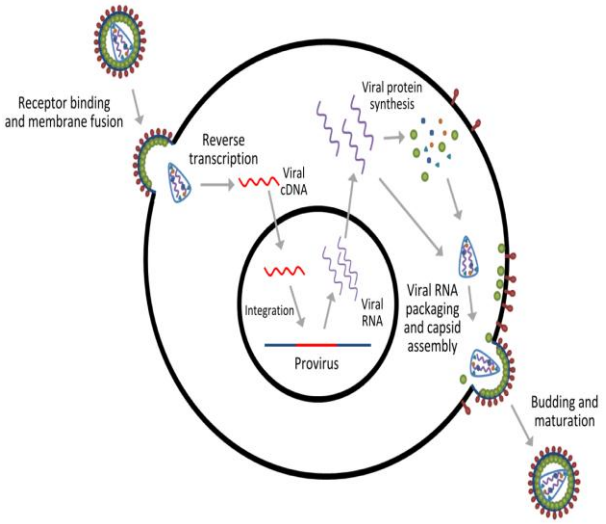

Fig. 3: Retroviral Replication.

Transmission and Virulence

Transmission of retroviruses occurs during exposure viral particles through blood due to injury or exposure to the bodily secretions of infected organisms during animal sports or butchering. It can also be transmitted through bites or scratch marks of pet animals. Cross-species transmission is enhanced by increased exposure and especially when there is a high prevalence rate of retroviruses (Arias, 2014). Apart from many other biological as well as environmental factors, viral and host characteristics also impact the efficiently of the infection. Viral capacity of adapting to a new host and surviving the various environmental and biological hurdles are all the factors that contribute greatly to the efficient infection spread among human populations (Peeters et al., 2014).

Ancient Viruses in Human Genome

As mentioned before, the endogenous retroviral sequences found in the human genome are basically the remains of ancient infectious diseases of the past. These crucial integrations occurred millions of years ago, and it has been discovered that around 8% of human genome consists of these viral sequences which make around 3 × 105 of these copies (Golon, 2008). There are three main group of human indigenous retroviruses; class 1: gamma retroviruses, class II: beta retroviruses and class III: spuma retroviruses. This nomenclature is based on one letter amino acid code which corresponds to tRNA primer involved in reverse transcription of viral genes. The structure consists of one open reading frame (ORF) and has gag, env and pol exons which are flanked by terminal repeats at 5' and 3' ends. This is the only feature common among endogenous and exogenous retroviruses (Mullins and Linnebacher, 2012).

Indigenous Retroviruses

Chromosomes in human genome have a number of endogenous retroviral genomes that makes up our normal genetic make-up and these sequences are present in other primates too. Most of these gene segments don't have any open reading frames so they are considered defective (Weiss, 2001). It is possible that the long terminal repeats (LTRs) present in them are active and could carry a number of carcinogenic elements. It is hard to create a direct link between these diseases and endogenous retroviral sequences because of the huge quantity and variation of the data available on human genome. It has been shown in some reports that many of these sequences transcribe some proteins and this has created a renowned interest on this topic. The phylogenetic linkage analysis (figure 4) shows a wide range of oncogenic elements linked to human indigenous retroviruses (Aminu, 2015).

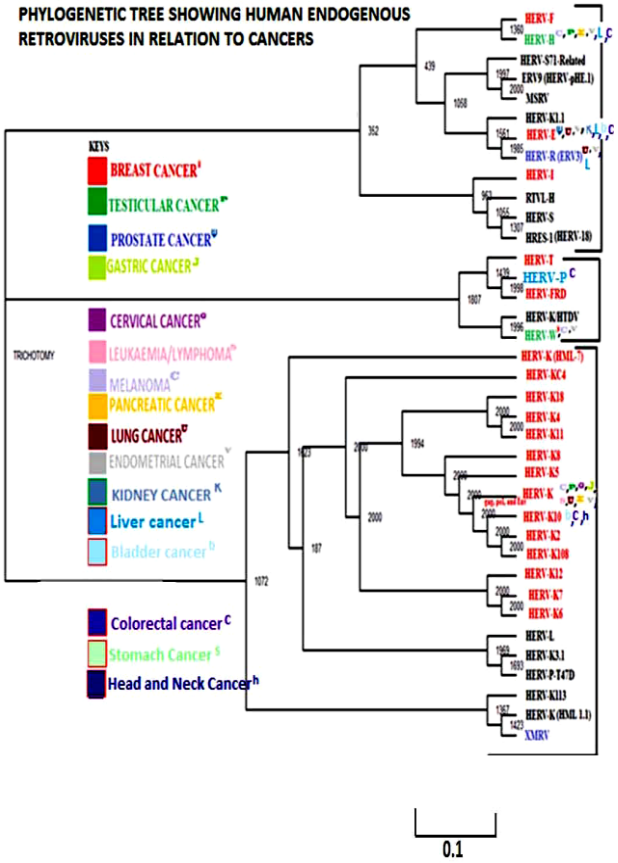

Fig. 4: Phylogenetic tree of human endogenous retroviruses involved in cancers.

Retroviruses and Cancer: Breast cancer, HIV, T-cell leukemia, Kaposi's sarcoma and others

There are a number of human cancers associated with retroviruses (Voisset, 2008). It is reported that the T-cell lymphotropic virus (HTLV-I) is the causative agent for the adult T-cell leukemia in human populations (Aminu, 2015). Human immunodeficiency viruses, HIV-1 and HIV-2 can indirectly cause Kaposi's sarcoma, cervical carcinoma and lymphoma by tuning on the DNA viral sequences present in these tumors to employ their oncogenic elements in order to cause cancer in the immunosuppressed hosts (Weiss, 2001).

Retroviruses and AIDS

In the year 1983, one retrovirus was identified in a patient with lymphadenopathy which is part of the AIDS as a syndrome. It originated the concept that this virus is the potential causative agent of AIDs as it is associated with lymphadenopathy. There were around fifteen thousand fatalities and twenty-six thousand cases reported that were AIDs related in the USA during 1981-1986. Now the fatality rates have been reduced significantly (Fanales-Belasio, 2010). There is a serological test which is an antibody to the virus is used in the diagnosis of AIDS and people who are at risk of having AIDS in their lifetime. There are many reasons that the virus itself is not the only AIDS causing element in this syndrome but a number of other factors are involved (Bolognesi, 1993). The overall ratio of carriers who are symptomatic is lower which proves that there must be another cause as the dormant period is of around five years and on the other hand there is a direct pathogen involved. There has been no gene identified that would cause the late AIDs as all genes replication is necessary for infection. There are very low levels of viral infiltration and along with the fact that viral expression is also lower, adds to the confusion about the real causative agent. The AIDS virus can be considered as the biggest occupational infection in people at risk as these viruses cause mostly the nonpathogenic or latent infections. The AIDS virion is considered as the indicator of sera with a potential of causing AIDS. All carriers manage to create an active immunity and this is why no vaccine has been effective so far as it has little benefit to the patients (Duesberg, 1987).

Table 1: Association of human diseases with retroviruses.

Disease	Reported evidence	Retrovirus(es) implicated
Cancer		
Breast cancer	EM, PCR, RT, FISH, Ab	MPMV, MMTV, HERV-K
Lymphoma	PCR	MPMV, HRV-5
Lung adenocarcinoma	Ag	Betaretrovirus
Thymoma	EM	Unknown
Ovarian carcinoma	EM, PCR, Ab, Ag	HIV-like, HERVs
Melanoma	EM, PCR, RT, Ab	HERV-K
Myeloproliferative disease	EM, PCR, RT	HERV-K
Testicular tumors	EM, PCR, RT, Ab	HERV-K
Prostate cancer	PCR, Ag, FISH	XMRV
Neurological disease		
Schizophrenia	PCR	HERV-W, HERV-K
Motor neuron disease	PCR, RT	HERV-W
MS	EM, PCR, RT, Ab, Ag	HERV-W, HERV-H
Chronic fatigue syndrome	EM, RT	"JHK-retrovirus"
Autoimmune and inflammatory		
RA	EM, PCR	HRV-5, HERVs
SLE	EM, PCR, Ab	HRV-5, HERVs, HIAPs
Mixed connective tissue disease	Nab	HIV-related?
SS	EM, PCR, RT, Ag	HIAPs, HRV-5
PBC	EM, PCR, Ab, Ag	MMTV-like
Graves' disease	EM, PCR, Ab	HFV, HIAP
IDDM	PCR, RT	HERV-K
Psoriasis	EM, PCR, Ab, Ag	HERV-E
Systemic sclerosis	Ab	HIAP-I

Ab= antiretroviral antibodies; Ag = retroviral antigen, Nab = neutralizing antibodies

Human T-cell leukemia virus type I

There are around ten to twenty million carriers of HTLV worldwide. The highest prevalence was reported in Southwestern Japan and the 20% of the adults are in danger of getting the infection. The seroprevalence rates go up as age increases and women have higher incident rates than men (Bhardwaj, 2014). The transmission occurs during exposure to contaminated blood products, blood transfusions or sharing needles. It also can be acquired through sexual contact or during the pregnancy. Vertical transmission of the virus is also observed in some cases. All case related studies show that this infectious disease continues throughout lifespan. Patients infected with HLTV-I usually show no clinical symptoms. Only some of the infected individuals develop HLTV related diseases and one of the most prevalent diseases is adult T cell leukemia lymphoma (ATLL). A number of complications occur that are mostly related to retinal degeneration and neurological diseases (Gordon, 2005).

Kaposi's sarcoma

Before AIDS became epidemic, it was thought that Kaposi's sarcoma was the most mysterious tumor in the world. It is more prevalent in Eastern Europe and Mediterranean populations and can be considered endemic in central and east Africa. Male prevalence is much higher and non-AIDS Kaposi's sarcoma occur mainly in males over the age of 60 (Ahmed and Muktar, 2011). KS has become the most common tumor in sub-Saharan Africa with the arrival of AIDS. KS's epidemiology after and before the advent of AIDS supported that a transmissible agent may be the cause of the tumor, and many agents including papilloma and cytomegalovirus viruses were put forward. On the other hand, a new virus, human herpesvirus or Kaposi's sarcoma-associated herpesvirus (HHV-8, KSHV) was discovered in 1994 and it proved to be an etiological agent for this disease (Norian, 2012). KSHV detection in HIV-positive patient's blood signals the development of KS31. It is indicated by surveys that KSHV has more occurrences in certain geographic regions and in groups where KS incidence is more. Therefore, KSHV unlike EBV is not an abundant herpesvirus. It is most commonly transmitted by tracks and saliva vertically in families. Both HIV and KSHV infection are highly important risk factors and dependent in the development of KS in AIDS (Weiss, 2001).

Breast cancer

Breast cancer is regarded as the most abundant and frequently occurring cancer type around the globe and it is also the second most fatal malignancy in female patients. Around 10% of these breast cancers are known to occur due to predisposed genetic elements and only one third are caused by genetic mutations such as BRCA2 or BRCA1 (Golan, 2008). Retroviruses have been investigated as the etiological element in human breast cancer too and the results align with the possibility of retroviral involvement in some of the breast cancer types but much is to be found out in this regard (Salmons, 2014). Scientists have found possible evidence for the potential involvement of a virus which extremely homologous to MMTV in the human breast cancer. Recent data has further confirmed the possible role of MMTV or its homologue HMTV agent. The apparent absence of the emerging MMTV-induced cancer tumors make us think that both viruses work together to cause this cancer and support each other. It could be finalized as a general acceptance in the coming years that retroviruses play an influential role in human breast cancer. There are a number researches being conducted in order to develop potential antiviral therapies and clinical diagnostic tools for breast cancer (Salmons et al., 2014).

Prostate cancer

It has been reported that the human prostate cancer has also been linked to Human endogenous retroviruses (HERVs) under new emerging evidence. Type K of the HERV and HML2 subtypes are the most intact retroviral sequence in the human genome as it is the most recently integrated (Rasmussen, 1996). It has been found to transcribe a number of functional fully or partially functioning viral proteins. To analyze the transcripts of HERV-K in cell lines of prostate cancer and pin point the HERV-K sequences in the human genome, RT-PCR and cDNA sequencing were carried out. The result showed presence of the sequences of HERV-K subtype (HML2) that coded transcripts in the cell lines of prostate cancer (LNCaP, DU145, PC3, and VCaP) (Mullins, 2012).

Multiple sclerosis

Multiple sclerosis is a neurological disease that is caused by a number of genetic and environmental factors. It is inflammatory in nature and involves demyelination (Rasmussen, 1996). Retroviruses have been considered for a long time as possible etiological agents in multiple sclerosis and it is believed that they may act as the endogenous human retroviruses. A series of tests was carried out for 50 endogenous retroviral loci in linkage with MS and it showed single nucleotide polymorphic markers near around specified locations. It showed in a number of reports that MS was associated with HERV-Fc1 locus, and another type of this disease which Is called Primary Progressive MS had no association with HERVs (Nissen et al., 2013).

Future Prospects of Anti-Retroviral Therapy

Retroviruses and cancer gene therapy

The new advancements in gene therapy techniques have created many opportunities for new treatment possibilities for difficult diseases. Although most effort is focused on single gene defects right now but cancer treatments have also been done in most of the clinical trials in gene therapy clinics. One example is of the genes encoding cytokines that have been explored in cancer treatments and as a pro-drug therapy using activated enzymes like herpesvirus thymidine kinase for the treatment of glioblastoma and other cancer tumors

(Aries, 2014). One of the vehicles used in this technology also so we can say that retroviruses have been also playing a key role in new treatment prospects for human diseases along with being the causative agents of many diseases as well. However, they possess an increased risk of causing cancer along with controlling it when they are integrated in the human genome for therapeutic purposes (Weiss, 2001). During the recent gene therapy trials, a number of retroviral vectors have been used as important tools in order to deliver nucleic acids in a number of cell types under many model systems. They have been proven as usable under laboratory conditions in tissue culture techniques as well as animal models. They have also been used in crucial clinical trials in new treatment perspectives. The retroviral system provides a heritable and stabilized integration for any DNA segment into target genome. It gives a permanent genetic expression and successful protein synthesis (O'Keefe, 2013).

Modern advancements in oncogenic viral research

With the tremendous advancements in the fields of molecular biology and genetic engineering, there are now many new approaches being adopted to understand the retroviral oncogenic mechanism. New sequencing techniques are highly accurate and can be done at reduced costs which provide a great opportunity in the crusade against oncogenic viruses (Moore and Chang, 2013). Now it is possible that only a short nucleic acid sequence can bring the discovery of a new tumor virus and it is highly possible that the number of such viruses will keep on increasing with the new discoveries. Now the previously thought causative agents can be eliminated easily as the reliability of such techniques increases. However, only identifying the causative virus is not enough and much work is needed in order to truly prove it. For example, MCC and head and neck squamous cell carcinoma are now believed to have multifactorial causative agents and are caused by both infectious and non-infectious factors (Sarid, 1999).

The advanced epidemiological tools that can employ highly detailed molecular biology data can be the new tools in pinning the actual causes of human cancers (Pfeffer, 2005). In the past, viruses were either totally ignored or were considered as the sole etiological agents in a number of cancers but now things are changing. Now at this point, we have eliminated and confirmed many oncogenic agents which have opened new doors in reducing the global burden of these diseases. Much is needed to be done as we are still far behind in producing immunological therapies and anti-latent viral drugs (Luo, 2009). In the coming decade, much will depend on our effective diagnostic measures, new treatment approaches and prevention mechanisms in reducing the global cancer burden.

CONCLUSION

Although viruses were ignored in the crucial battle against human cancers, the new research and discoveries in the field of oncology have given a special place to oncogenic viruses and retroviruses. The cancer associated viruses are now analyzed in great detail and new etiological agents have been discovered with the help of new techniques. Many retroviruses can also be used in the emerging gene therapies and trials have been conducted in order to see the effect of these treatments in clinical settings. The new technologies have given a deeper insight into mechanisms behind cancer causing elements in human genome and their linkage to both exogenous and endogenous viruses. New treatments and therapeutic approaches are being adapted to combat cancerous diseases that are expected to change the current status of cancer research and treatments. There are many hurdles to overcome in this field, including effective vaccination and immunological therapies. Diseases like HIV are still the reason of countless fatalities across the globe and there is no effective vaccine available. Despite the growth in this field, much work is needed to be done in order to truly apply the new findings into clinical practices throughout the world, only then we can have a fighting chance against growing global cancer burden.

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